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RENAL DISEASES: SOME FACTS AND PROBLEMS *

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THIS discussion will include some comments on the classification of renal diseases; the pathogenesis and prognosis of acute diffuse glomerulonephritis; the sequence of events in hypertensive vascular disease or "essential" hypertension, and some of the diagnostic and therapeutic implications; the status of diabetic glomerulosclerosis; and the rôle of the great group of functional diseases of the kidney with special emphasis on circulatory or hemodynamic disturbances, as well as on affections of the renal tubules. Obviously, only the highlights of these major aspects of the field of organic renal disease and dysfunction can be covered.

CLASSIFICATION

You will notice that the classification of organic medical renal diseases (table 1) follows generally the accepted views of Volhard and Fahr,[1] Fish-

TABLE I

Classification

A. Organic Renal Diseases

1. Glomerulonephritis—Acute; chronic
2. Glomerulonephrosis—Lipoid; amyloid
3. Glomerulosclerosis—Arteriolar; diabetic
4. Glomerulitis—Toxic; embolic; thrombotic; allergic
5. Pyelonephritis—Acute; chronic
6. Vascular—Arteriolosclerotic; inflammatory (allergic)
7. Tubular—Necrotizing; obstructive; degenerative
8. Congenital anomalies

berg,[2] Addis and Oliver,[3] and Bell.[4] For the sake of convenience in thinking about pathogenesis and clinical syndromes, I have rearranged the grouping somewhat,[5] e.g., in classifying lipoid nephrosis as a glomerular rather than

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tubular disease since abnormal glomerular permeability to plasma protein is probably the primary defect in this disease. For similar reasons, amyloid renal disease is included under the same heading and, perhaps, the specific toxemia of pregnancy may also be classified under glomerulonephrosis although the present working classification will probably have to be modified as soon as we learn more about the rôle of steroid hormones, their site of origin and their chief site of action in the body in relation to the edema and hypertension of the toxemia of pregnancy.

In the case of the organic vascular diseases of the kidney (among which embolism and thrombosis should be included) there is some duplication in the classification because of the desirable emphasis on glomerular involvement in the form of glomerulosclerosis. This distinction is not merely a pathological one but has definite clinical implications in regard to urinary changes and impairment of renal function. Our present methods of diagnosis with the possible exception of the estimation of renal blood flow and filtration fraction [6] in subjects without cardiac failure, are not sufficiently sensitive to detect renal vascular disease before glomerular changes have developed; hence, when we make a diagnosis of renal arterio- or arteriolosclerosis, benign nephrosclerosis, hypertensive renal vascular disease or arteriosclerotic Bright's disease—whichever designation you prefer—we really mean glomerular sclerosis associated with, or secondary to, hypertensive disease. To be sure, this change in the glomerular vasculature is bound to reflect itself in functional and, later, organic changes in the corresponding tubules, because of the arrangement of the renal circulation.

You will observe that the term "glomerulitis" has been substituted for "glomerulonephritis" to cover the focal toxic, embolic, thrombotic or allergic inflammatory lesions of the glomeruli, and that this whole group has been separated from glomerulonephritis. This leaves us without the clinical diagnosis of "focal glomerulonephritis," popular in many quarters. I believe that there is now considerable evidence, clinical and pathological, to make the use of the diagnosis of "focal glomerulonephritis" very dangerous from the standpoint of both treatment and prognosis.

Clinical experience has shown that the Volhard and Fahr [1] concept of focal glomerulonephritis was based partly on inadequate follow-up of patients, on underestimation of the significance of the urinary findings in the so-called latent stage of nephritis, and certainly on a somewhat dogmatic a priori concept of the cardinal symptoms of acute diffuse glomerulonephritis. If we assume with Volhard that hypertension is an absolute sine qua non of acute diffuse nephritis, then, of course, many cases of mild diffuse nephritis but without hypertension, edema or gross renal impairment will be misdiagnosed as focal glomerulonephritis. Careful follow-up on such cases with adequate study of urinary sediment and renal function has disclosed a distressing proportion of persistent nephritis which, after some or many years, finally resulted in the typical end-stages of diffuse glomerulonephritis.

Furthermore, Chabanier and his associates [7] made biopsies on the kidneys of a significant number of patients with various types of glomerulonephritis; all with an alleged focal nephritis revealed typical diffuse glomerular inflammation, indistinguishable from the lesion found in a parallel series of patients with the clinical picture of diffuse nephritis of the Volhard and Fahr classification. One should be particularly skeptical of the diagnosis of recurrent focal nephritis in view of the prevalence of exacerbation of diffuse glomerulonephritis during upper respiratory infections.

Furthermore, the diagnosis of focal nephritis when based on albuminuria and hematuria discovered during or after an acute infection, always carries with it the hazard of overlooking the numerous and important urologic causes of gross or microscopic hematuria. It is for these and other cogent reasons that a clinical diagnosis of focal glomerulonephritis should never be made. If there are red blood cell casts in the urine, the source of the hematuria must be glomerular and the differential diagnosis will then include the various causes of glomerulitis. Obviously, the entire clinical picture of the underlying disease must be taken into account. On the other hand, in certain obscure conditions the demonstration of urinary changes compatible with glomerulitis may settle the diagnosis in favor, let us say, of allergic vascular disease, visceral lupus erythematosus or subacute bacterial endocarditis.

Acute Glomerulonephritis

A. Immunology. Just a few remarks on the nature of the immunological reactions which lead up to the development of acute diffuse glomerulonephritis in man. The overwhelming association with hemolytic streptococcal infections [8]; the latent period between the acute infection and the onset of acute nephritis; the permanent immunity to nephritis after recovery on the one hand [9] and the persistent allergic reaction of the kidneys to reinfection with hemolytic streptococci in the less fortunate group that fails to heal after the initial attack [10]; and, finally, the experimental production of acute diffuse glomerulonephritis in laboratory animals by the Masugi [11] method of developing antibody to kidney protein, although in a foreign species—all this evidence points strongly, if not conclusively, to the theory that acute nephritis in man represents an allergic reaction occurring in the kidneys, presumably as the result of an auto-immune response to kidney protein rendered antigenic by the toxic or denaturant action of some streptococcal product, or combined streptococcal-tissue product, as suggested by Schwentker and Comploier.[12] A combined or complex auto-antigen resulting from a sulfa drug and kidney protein may similarly be responsible for the polyarteritic or periarteritic nodosa-like lesions produced in rabbit kidneys by Rich,[13] and found in some human kidneys after sulfa treatment. The analogy can be broadened to include many of the cases of glomerulitis occurring during generalized diseases of presumably allergic origin.

However, it should be noted that even the Masugi nephritis is not necessarily the simple kidney antigen-kidney antibody reaction, as has been well pointed out by Kay [14] in experiments on rabbits. He explains the latent period of the Masugi reaction on the basis of secondary antibody formation to foreign serum protein. Actually it is impossible to produce anti-kidney antibodies in the same species by Masugi technic. According to the Caveltis [15] the kidney acts as a hapten and the streptococcus as the protein carrier in the auto-antibody response which they have reproduced for the first time (table 2). The human situation may also be far more complex

TABLE II

Immunologic Mechanism of Glomerulonephritis

A. Experimental:

1. *Masugi's heterologous "nephrotoxin":*
   Kidney antigen → anti-kidney serum
   Anti-kidney serum + kidney → allergic nephritis
2. *Kay's explanation of process:*
   Rabbit kidney antigen → duck anti-kidney serum
   Duck anti-kidney antibody + rabbit kidney → harmless complex (H.C.)
   Normal duck serum antigen → rabbit anti-duck antibody
   Rabbit anti-duck antibody + H.C. in rabbit's kidney → allergic nephritis
3. *Caveltis' effective mechanism:*
   Streptococcus + kidney = complex auto-antigen
   Auto-antigen → anti-kidney auto-antibody
   Auto-antigen + auto-antibody → nephritis

B. Human: As in A3, first suggested by Schwentker and Comploier

than is ordinarily assumed, and, until more direct evidence is obtained as to the nature of the antigen and antibody involved in this remarkable reaction, final judgment must be withheld.

We are still a long way off from preventing acute glomerulonephritis by the administration of some anti-histaminic agent. It is not even certain whether the very early administration of adequate doses of sulfa or penicillin in acute streptococcal upper respiratory infections diminishes the small incidence of acute diffuse nephritis. It is very difficult to obtain reliable statistical material on this subject.

The rôle of diet in the treatment of acute glomerulonephritis may also be considered from the immunological viewpoint if one bears in mind Cannon's [16] experiments on the influence of dietary protein on the formation of antibodies. Conceivably, any measure which sharply reduces or suppresses the ability of the body to respond to an antigen may, to this degree, reduce the extent of the anaphylactic reaction that depends on the combination of so much antibody with so much antigen. A very low protein diet early in acute nephritis may retard the formation and accumulation of sufficient antibody to maintain the dangerous level of the allergic reaction in the kidney. On the other hand, simultaneous suppression of antigen formation by early

chemotherapeutic inhibition of bacterial growth will also help in reducing the reactant substances. It is obvious that little can be expected on this basis from therapeutic dietary restriction after the glomerulonephritis has been well established. Addis [17] has long claimed that the fate of the patient with acute nephritis, insofar as renal recovery is concerned, is settled within the first week or two. Protein in the diet during this period may well have more far reaching effects than simple reduction of renal excretory work. But all this is largely speculation and more facts are needed.

B. Diagnosis. The importance of an early diagnosis of acute nephritis cannot be overestimated. A simple consideration of the sequence of events between the onset of the bacterial infection and the occurrence of acute nephritic symptoms or signs indicates clearly that it is the duty of the physician to examine the urine carefully at intervals of one, two and three weeks after the onset of acute streptococcal infections. The usual analysis of the urine obtained at the first visit, at the height of the infection, is of value only as a control specimen and to detect the occasional case of mild chronic active or latent glomerulonephritis acquired at some time in the past. It must be emphasized that concentrated urine specimens should be obtained after 12 to 18 hours of dehydration, and that centrifugation is essential. Under these conditions, minor transitory urinary changes may be detected at the right interval (one to three weeks after the beginning of the acute infection) in 5 to 10 per cent of young individuals with proved hemolytic streptococcal infections. Perhaps only 1 per cent will develop clinical acute diffuse glomerulonephritis. It is the failure to test the urine at the right time that permits the accumulation of instances of chronic glomerulonephritis of so-called idiopathic or insidious onset. Acute and chronic glomerulonephritis have the same etiology, but it is unrecognized or overlooked in the latter, due largely to lack of obvious symptoms in the vast majority of post-infectious acute nephritis. I do not believe that there is a non-specific chronic nephritis in children; as Aldrich [18] has claimed. It is rather the result of an undetected, mild but unhealed, acute nephritis. The story of scarlet fever acute nephritis with its practically non-existent chronic form is valuable evidence in favor of this view.[19]

C. Prognosis. There has been a great variety of opinion concerning the prognosis of acute glomerulonephritis with a typical clinical syndrome. In some series as high as 70 or 80 per cent of the cases progressed into a chronic irreversible stage; in other series, almost 90 per cent recovered completely and, presumably, permanently. One of the great difficulties in evaluating much of the data in the literature is the means of distinction between the initial acute nephritis and exacerbations, during some infection, of previously unrecognized chronic nephritis. Another problem has been the nature of the follow-up examination. When the Addis sediment count was first popularized, the prognosis of acute nephritis suddenly became very gloomy, even in children, in California.[20] The same method used in New York by the same

author gave no such dire results.[21] One of the reasons for this difference must have been the nature of the clinical material in the California clinic. Many of the cases were probably unhealed or reactivated glomerulonephritis, without control observations prior to their admission to the hospital; hence the prognosis was much poorer than in patients seen during the initial acute nephritis. Some of the patients may have been selectively referred for examination because they were not doing well, while the recovered group remained at large, and outside of the statistics. These and other points are well discussed in a recent review by Rudebeck,[22] whose own data are illustrated in table 3.

TABLE III

Prognosis of Acute Post-Infectious Glomerulonephritis *
(J. Rudebeck, Acta med. Scand., 1946)

		%
Total patients (ages 11–67) (admitted within 3 mos. of onset)	318	100.0
Deaths, acute or subacute	21	6.6
Chronic nephritis **	43	13.4
Complete recovery	254	80.0
(under age 30, in 90%)		
(over age 50, in <50%)		

* Cases with scarlet fever, diphtheria or without history of acute infection excluded.
** 25 dead in 1½ to 18 years from onset. 18 living, 4 to 31 years of nephritis.

Rudebeck deliberately excluded cases without a history of acute infection at the onset of the nephritis in order to avoid the pitfall of latent or mild chronic nephritis. His material otherwise is similar to the accumulated data from other sources in that the preceding infection was upper respiratory in 88 per cent, erysipelas or pyoderma in 5 per cent, pneumonia and rheumatic fever in about 2 per cent each. He personally reëxamined over half of the patients, carrying out Addis counts on the urine sediments of 75 per cent of this group. He found that if the urine was normal one year after the patient was asymptomatic, there was only a slight statistical chance of a return of abnormal findings; in the case of the blood pressure, a three year period of normality was conclusive. In the older age groups, a persistent hypertension in the absence of urinary changes made interpretation difficult, particularly when the blood pressure level prior to the acute nephritis was often unknown.

His report confirms the view that age is an important factor in the prognosis of acute nephritis. It agrees closely with data of Schwarz et al.,[23] on 244 children with acute nephritis—84 per cent recovery, 5 per cent death, 12 per cent chronic. It also seems to indicate that diet, level of blood pressure, amount of edema or albuminuria and even the early institution of bed rest are of little influence on the prognosis. However, the severity of the nephritis, as measured by degree of renal insufficiency, and its duration, are important in determining the tendency to chronicity. Severe oliguria or anuria and cardiac failure are of significance only in the immediate mortality

and not in the ultimate outcome of the disease. Rudebeck concludes that the course of acute nephritis is little affected by medical treatment, but probably determined by the original injury. Residual symptoms, so-called, must be taken seriously; they must have disappeared before the nephritis can be considered as healed. He considers the diagnosis of focal glomerulonephritis as dangerous, for the reasons I indicated earlier.

The remarkable absence of chronic nephritis after the acute nephritis complicating scarlet fever [19] has never been adequately explained, although one is strongly tempted to attribute this result to keen medical and lay awareness of the possibility of acute nephritis; hence, early diagnosis and appropriate symptomatic treatment, of which bed rest is probably the most important. To what extent the immunological reaction to the streptococcal erythrotoxin contributes to renal recovery cannot be determined from the available knowledge of this process.

Hypertensive Vascular Disease

If we accept Goldblatt's [24] hypothesis that presenile renal arterio- and arteriolosclerosis are the primary factors in "essential" hypertension, we have before us the most common and most important organic disease of the kidney —in fact, the most common and most important human organic disease. If, on the other hand, we agree with the large group of students of hypertension, who claim that the initiating factor of general vasoconstriction is unknown,[25, 26, 27] perhaps psychogenic or neurogenic, and that the disturbance in renal hemodynamics is part of this functional vascular derangement, then we must consider high blood pressure as partly a manifestation of functional renal disease, ultimately ending in organic renal vascular disease through as yet unknown intermediate or parallel phenomena. The various alternatives are illustrated in table 4.

Table IV

Mechanism of "Essential" Hypertension

	Goldblatt Theory	Other Theory
1.	Unknown stimulus	Unknown stimulus
2.	Renal arteriolosclerosis	General vasoconstriction
3.	Renal dyshemodynamics	Arterial hypertension
4.	Increased renin, etc.	Renal arteriolar constriction
5.	General vasoconstriction	Reduced renal blood flow
6.	Arterial hypertension	Increased renin, etc.
7.	Arteriolosclerosis	Arteriolosclerosis (renal)

In favor of the functional theory are the perfectly symmetrical changes in glomerular and tubular function demonstrated in hypertensive patients by

Chasis and Redish,[28] the bilaterality of pathology or complete lack of it in renal biopsies on hypertensive patients shown by Castleman and Smithwick,[29] and the evidence for predominance of neurogenic factors early in human hypertension.[30] In the experimental Goldblatt animal, however, there is some evidence to the contrary—i.e., late central or neurogenic disturbance in blood pressure regulation with maintenance of an elevated pressure even after removal of the constricted kidney.[31] Goldblatt [32] does not accept these results for technical reasons and the matter is still sub-judice. It is to be hoped that the rapid development of pharmacologic hemodynamic tools in the form of the various adrenolytic, sympatholytic and autonomolytic drugs of the Fourneau or methylbenzodioxane [33] tetraethylammonium [34] or dibenamine [35] series will soon enable us to draw up a percentage composition table for hypertensive patients in which we could indicate what percentage of a given subject's mean blood pressure is due to ordinary sympathetic vasomotor tone; what percentage to momentary epinephrine or sympathin release due to excitement or exercise; what percentage to excessive continuous or paroxysmal release of epinephrine from an adrenal medullary tumor or other pheochromocytoma; what percentage to excessive renin or its products; what percentage to excessive delivery of salt-retaining and other vasopressor steroids from the adrenal cortex or elsewhere, and what residual percentage from organic narrowing of numerous small arteries and arterioles. Only by this complete pharmacologic analysis of arterial blood pressure shall we ultimately arrive at a satisfactory pathogenesis and, probably, rational therapeutics of hypertensive disease in man.

While awaiting this happy day with apneic respiration, it may not be amiss to point out the present confusion in the minds of many in regard to the harmfulness or harmlessness of hypertension per se; the arguments pro and con as to the relation between high blood pressure and general or renal arterio- and arteriolosclerosis—from which stems the important consideration as to the utility or futility of interrupting the sympathetic nervous pathways and, hopefully, lowering the blood pressure for a shorter or longer period. If, as Goldring and Chasis [26] say, the organic vascular disease proceeds more or less independently of the hypertension, are we not wasting the impatient energies of our surgical confreres? Perhaps—but we are learning some things about human neurovascular physiology.

Furthermore, many a general practitioner and many a young certified internist exclaim—"But what else can you do for the hypertensive patient?" They are, of course, too modest to estimate properly the great value of careful medical examinations of the psychosomatic type and the rôle of their own reassuring personality in maintaining a fair state of health for decades in many of their patients. They do not, like some surgeons, prophylactically exclude from their mortality and morbidity lists all patients over 50, over 45, over 40 or is it 35 years today; or all patients with established organic disease of the heart, retinal vessels, brain and kidneys; or patients with a host

of other items that bring the number admitted to candidacy for sympathectomy down to about 5 to 10 per cent of the average number seen and treated by the medical man. Speaking for medical treatment, perhaps we are not doing so badly as it sometimes seems.

However, we must face reality in this problem of hypertension and, therefore, turn all our energies in the direction of learning more about the mechanism of regulation of blood pressure in the normal and hypertensive states. A mass of evidence is accumulating from various directions that sodium retention in some manner is decisive in both experimental and human hypertension.[36, 37] At least one of the effective means for lowering the blood pressure involves sodium depletion. The virtue of Kempner's [38] rice, fruit and fruit-juice diet undoubtedly resides chiefly in the low sodium content. The low protein and low fat intake, according to Grollman,[37] Dock [39] and some of our own observations, apparently have little to do with the therapeutic effect except that the protein of rice is exceptionally good cereal protein and well utilized. As a corollary of the studies on Addison's disease and the rôle of Doca (desoxycorticosterone acetate) in promoting retention of salt and water and causing or restoring hypertension if given in excessive doses, Perera [40] and his associates [41, 42] have recently shown that patients with essential hypertension react to sodium restriction as though they had excessive Doca within them and that they develop rapid rises in blood pressure above their basic, control hypertensive figures when they are given Doca plus extra salt in amounts which in the normotensive subjects would require weeks to yield significant changes.

What this means in regard to the adrenal cortical rôle in hypertension and whether it supports Selye's [36] theory on the damaging renal, glomerular and vascular action of Doca plus salt, cannot be settled at present. But for those who believe in the psychogenic or neuro-endocrine theory of origin and perpetuation of hypertension, there are only a few feet of vascular and nervous tubing between the cortical-hypothalamico-pituitary axis and the adrenal cortex. Let us hope that it will not take too long to bridge the remaining gaps in our knowledge of the mechanism.

Diabetic Glomerulosclerosis

It is with deep humility, because of profound ignorance, that I approach this subject. Having had the somewhat frustrating experience of observing the late stages of 15 classical instances of this condition, with 11 autopsies, in the last five years at the Montefiore Hospital, I can only urge those of you who deal with diabetics in the first decade of their disease, to watch them as closely as possible for any clues as to the initiation of glomerulosclerosis. Two of our patients died in their late twenties. Dolger [43] has reviewed 25 years of experience with the management of 200 diabetics whose disease began before age 50. Among these were 55 juvenile diabetics, seven of

whom died, three with the Kimmelstiel-Wilson syndrome. The distressing feature is that regardless of the type of management employed, retinal hemorrhages developed in all his young patients within six to 22 years. Half of those with retinopathy had hypertension, and 30 per cent had albuminuria—in short, the makings of a diabetic glomerulosclerosis. You can appreciate the havoc caused by this disease when you learn that 14 per cent of Dolger's 200 diabetics were partially or totally blind, and that in some of our older patients impairment of vision was the first reason for seeking medical aid.

The diabetes may be so mild that a glucose tolerance test may be required for diagnosis. The blood pressure may not be elevated because of previous myocardial infarction. There may be no history nor presence of edema in rare instances of otherwise typical syndrome. The edema may be nephrotic in younger individuals with massive proteinuria and hypoalbuminemia and fair renal function. However, in patients over 55, proteinuria usually does not exceed 5 to 10 grams a day, the plasma albumin is often normal or only rarely below 3.5 grams per cent and the real reason for the patient's edema is congestive heart failure with elevated venous pressure and renal insufficiency, eventually progressing to full uremia.

Since all these patients show considerable renal arteriosclerosis and arteriolosclerosis at autopsy, it is not surprising that the specific nature of the syndrome was not fully appreciated until 10 years ago.[44] Given a patient over 50 with diabetes and retinopathy, one look at the urine sediment may be sufficient to make the diagnosis of diabetic glomerulosclerosis, if one finds some lipoid or fatty cells or casts. A polarizing device is unnecessary for their recognition although it makes a pretty demonstration. Any good technician can be trained within a few days to spot the lipoid cells or casts with the low power objective. In younger diabetics one has to consider chronic glomerulonephritis in the differential diagnosis. In some tuberculous diabetics, amyloidosis of the kidney may give rise to fatty cells and casts. The beauty of this simple method of diagnosis lies in the fact that hypertensive renal vascular disease, or nephrosclerosis, so commonly associated with diabetes in older individuals, does not produce a similar urinary sediment in this one respect. In fact, the finding of albuminuria and fatty cells by a reliable technician may furnish the first clue to the existence of diabetes in an older patient with congestive heart failure.

It is in the doctor's office and in the outpatient clinic for diabetes, that the beginning of this vascular complication or integral part of diabetes mellitus will have to be studied. Diabetic glomerulosclerosis is more important numerically than chronic glomerulonephritis, and there is every reason to believe that its incidence will continue to increase as its recognition spreads and as more diabetics live on for decades with their metabolic disease. We must vigorously attack the problems of the relation of the diabetes to the vascular disease—arterial, venous and capillary. The approach to this task is not simply one of this or that type of diet.

Functional Renal Diseases

In these days of increasing emphasis not only on the pathological physiology of disease but especially on the functional pathogenesis of the earliest stages of organic disease, one need make no apology nor give any argument for the inclusion of the great and important group of functional disturbances or diseases of the kidney in the classification (table 5). It is the growth

Table V

Classification

B. Functional Renal Diseases

1. Vasoconstriction—
   - Hypertension
   - Cardiac failure
   - Albuminuria
   - Early shock
2. Tubulovascular—
   - Severe shock syndromes due to
   - Hemorrhage
   - Crush
   - Burns
   - Dehydration
3. Tubular—Hormonal—
   - Diabetes insipidus
   - Addison's disease
   - Cushing syndrome
   - Hypertension (?)
4. Tubular—Metabolic—
   - Renal diabetes
   - Fanconi syndrome
   - Other defects

of the tree of knowledge of renal hemodynamics, glomerular filtration, tubular reabsorption, tubular excretion and tubular metabolism so beautifully nurtured by renal physiologists in the last three decades, that is now yielding splendid fruit in applications to the clinical problems of shock, congestive heart failure, diabetes insipidus, adrenal cortical disease and hypertension, to mention only the most important.

It is nevertheless a remarkable fact that by stretching one's hemodynamic theories just a little here and there, it is possible to subsume the most important and most prevalent of human diseases, acute and chronic, under the heading of functional renal diseases. To take the chronic group first, a good case can be, and has been made out for essential hypertension as a disturbance in renal hemodynamics. I have already alluded to this in table 4. More recently, thanks to the work of Warren and Stead [45] and Merrill,[46] the edema of chronic congestive heart failure has been claimed to depend chiefly on reduced glomerular filtration, secondary to renal vasoconstriction, in turn presumably compensatory to reduced cardiac output, whether absolute or relative; in short, "forward failure" (table 6). If the kidney were not so generous in giving up a large part of its own huge blood

flow, for the benefit of more vital structures, cardiac patients would not develop edema so readily when their hearts fail. The real trouble, as my colleagues Mokotoff and Ross [47] have shown clearly, is that the renal tubule of the patient in congestive heart failure behaves exactly like a good normal tubule should—it reabsorbs the same amount of sodium (13.3 milli-equivalents per 100 c.c. of glomerular filtrate), as the tubule of a non-cardiac subject on a similar diet. Otherwise the serum sodium would not remain constant. Therefore, any reduction in glomerular filtration is immediately reflected in a much reduced clearance or excretion of sodium. If, in an edematous cardiac patient, the glomerular filtration rate is artificially increased toward normal by intravenous injection of aminophyllin, the excretion of sodium in the urine temporarily reaches the same rate as it would in the control subject with a similar glomerular filtration and serum sodium level, because the renal tubule keeps on reabsorbing the 13.3 milli-equivalents of sodium for every 100 c.c. filtrate, allowing the excess above this "threshold" to escape into the urine. When a mercurial diuretic is given, the filtra-

TABLE VI

Cardiac Renal Dysfunction

1. Myocardial insufficiency
2. Decreased cardiac output (relative or absolute)
3. Decreased blood flow
4. Renal vasoconstriction ↑ (excessive; efferent ⇆ renin release)
5. Low glomerular filtration
6. Low salt clearance
7. Edema; hypervolemia
8. Venous hypertension

For "backward failure" read 1→ [8] → 7, 5, 3

Exercise aggravates 4→5→6→7; 1→ [8] → 7

tion of sodium is unaffected but the tubule is slightly "poisoned" and falls below its usual reabsorptive capacity for sodium; hence a salt and water diuresis. You see, therefore, how easy it is to oversimplify the edema of congestive heart failure by blaming it on the blind performance of ancient homeostatic duties by perfectly normal renal tubules which, so to speak, cannot fish beyond the depth of their own glomerular filtrate and blood capillaries, nor ever cast their cytoplasmic rods into the distant water-logged tissue spaces.

Actually, there is a little more to cardiac edema than the function of the kidney as Landis [48] has shown, but this is not the time to discuss the other

aspects of the intriguing old problem except to reëmphasize the practical implications as to control of salt in the diet of patients whose glomeruli cannot possibly filter out sufficient salt to exceed the reabsorptive capacity of their proximal and distal tubules. If you ask "Why not simply give a few more injections of a mercurial diuretic?"—the answer is: "Of course!", provided the patient's rate of reaccumulation of edema is reasonable. But when one, two or three injections a week are required to rid the body of 10 or 15 grams of salt and its associated water, is it not more sensible to reduce the dietary content of salt from 5 or 6 grams a day to 1 or 2 grams and slow down the rate of accumulation correspondingly? The virtues of adequate salt restriction have been rediscovered recently in various parts of the country from Montana [49] to Massachusetts [50] and, as more and more cardiac patients live on for years or decades with congestive failure, it will become more and more necessary to re-indoctrinate physicians, dietitians and patients in the details of low salt diets. Recent re-analysis of the sodium content of many natural and standard prepared foods by the rapid and precise flame photometer method,[51] has furnished a somewhat more liberal basis for a palatable salt poor diet. The development of sodium-free, reconstituted milk has been helpful.[51] The problem of a substitute for salt has not yet been solved, but it should not be insuperable in the near future if enough chemical and pharmacological aid is enlisted.

Tubulo-Vascular Syndrome

Renal vasconstriction, as already pointed out, is a rather general reaction occurring whenever the efficiency or integrity of the circulation is threatened by cardiac injury or disease, skeletal trauma, hemorrhage, dehydration, comas, etc. Presumably, the immediate effect of this diversion of blood from the kidney is to make more of the low cardiac output available to vital areas—heart, brain, lungs, liver. So far so good. A few hours of oliguria or even anuria is not a catastrophe; and it is a fact that the kidney can safely stand complete interruption of its arterial blood supply for 20 or 30 minutes. But when the state of renal vasoconstriction and marked ischemia persists for 12 to 24 hours or longer, something apparently happens to the vitality of the tubular epithelium and a whole series of dysfunctions arise, with or without structural alterations, that may lead irreversibly to uremia and death even though the original injury to the body or to the circulation may already have been corrected. This is well exemplified in the late renal deaths in the crush syndrome, after incompatible blood transfusion reactions, in post-operative reactions, in the so-called hepato-renal syndrome, various infections and intoxications, metabolic comas and other conditions too numerous to mention.

One may look upon this variety of conditions from a unitarian or multiple point of view. Furthermore one may consider them from the morphological or functional sides. Among the pathologists there has been a strong tendency recently to attribute much of the serious renal dysfunction to degen-

eration or obstruction of the distal convoluted tubules. Both Oliver [52] and Lucké [53] have adduced striking histological and histochemical evidence for this concept. Lucké has used the term "lower nephron nephrosis" to designate this syndrome, which he considers the most frequent form of fatal renal disorder among military personnel. In civilian life, auto accidents and industrial, agricultural and mining injuries must furnish a large number of hitherto poorly recognized cases. It should be noted that the pathologist's emphasis on the distal convoluted tubule requires physiological confirmation and that it does not exclude dysfunction of the proximal convoluted tubule as the main disturbance.

Maegraith [54] in 1944 coined the term "tubulo-vascular syndrome" and reached the conclusion that only renal anoxia could fully account for the wide variety of clinical conditions associated with oliguria, anuria and uremia. Like some other investigators, he minimized the rôle of mechanical blockage of tubules by casts, débris, crystals, pigment or proteins and was unimpressed by the evidence for the nephrotoxic action of various hypothetical agents. While his unitary concept of renal anoxia is an attractive one in view of the high oxygen requirement of the kidney, it still lacks direct experimental proof, and may be too sweeping a generalization.

The dividing line between the tubulo-vascular functional disturbances and the organic chemical nephroses or necroses of tubules is a tenuous one, and, perhaps, of only temporal or quantitative significance in many instances. The important unifying feature is what McCance and Lawrence [55] have aptly called "functional disorganization" of the kidney. The renal tubule loses its highly selective ability to reabsorb certain elements and to discard other substances in the glomerular filtrate. Salt, non-protein nitrogen, glucose, water, acids, bases, etc., may diffuse back completely through the disorganized tubule especially since filtration is very low on the one hand, and on the other hand, there is often some blockage of distal and collecting tubules by casts, pigment, débris, sulfa and what not. Interstitial edema of the kidney, with a tense capsule, may add further to the functional confusion.[56] The net result is severe oliguria or anuria and uremic coma, superimposed on the patient's other troubles. The disturbance is often not recognized unless urine volume and concentration and the blood chemistry have been closely watched by the physician during his preoccupation with the patient's cardiac, peripheral vascular, pulmonary, cerebral or skeletal situation.

Time is of the essence if renal recovery is to result from treatment. There are only two alternatives—death from uremia or complete recovery. Chronic intermediate stages do not seem to occur. Furthermore, amazing blood chemical changes and dire general effects may be produced by indiscriminate infusion of this or that solution, due to slow response or lack of selective response by the kidneys. In severe instances in the past, after urinary tract obstruction was excluded by ureteral catheterization and the usual medical measures had failed, decapsulation had to be considered, often

too late. Today, the ingenious and well-tested artificial kidney of Koiff [57] should be a godsend for patients with previously good kidneys, because it is the ideal heroic treatment to tide the patient over the renal "blitz." Lacking this device, the alternative, although a rather poor one, is peritoneal irrigation for several days.[58] Even a brief experience with this method or any method for restoring renal function in this group of tubulo-vascular conditions, is sufficient to impress one with the profound wisdom and specific gravity of the old saying about the ounce of prevention. Therefore, the first line of attack in the treatment of medical or surgical shock, after pain, anoxia and hemorrhage have been counteracted, is meticulous provision of proper conditions and materials for kidney function, leaving nothing to guess work. The 24 hour urine volume, measured at each voiding or every six hours by catheter, may be far more important than the rectal temperature, or the pulse rate. Decisions as to need for parenteral fluids should be made several times, not merely once, in 24 hours.

The only safe diuretics in this condition of renal ischemia and tubular damage are a normal circulating and well-oxygenated blood volume, a balanced electrolyte and glucose solution preferably hypotonic as to salt, unless the serum values are quite low, with enough bicarbonate or lactate to counteract acidosis present or expected, and in the case of children with diarrheal states, with adequate potassium.[59] Mercurial diuretics are mentioned only because they should be strictly avoided. They have no place in the treatment of the tubulo-vascular syndrome. The plasma volume, hematocrit, plasma protein and serum sodium, chloride, CO_2 and potassium, as well as the blood urea or non-protein nitrogen, must be determined at appropriate intervals to aid in the intelligent use of the therapeutic procedures just outlined. Otherwise, one pours bottles into the circulation in the dark and enjoys or suffers the chance consequences.

Specific Tubular Dysfunctions. Just a few comments on the specific or isolated tubular dysfunctions associated with striking clinical syndromes, such as diabetes insipidus, Addison's disease of the adrenals, its opposite number the Cushing syndrome, renal diabetes, the Fanconi syndrome, and acidotic osteomalacia. It is evident that the first two diseases represent the effect of lack of hormones produced outside the kidney, but with the chief symptoms resulting directly from the renal functional disturbance. In other instances, like the Cushing syndrome, renal symptoms form only a small part of the clinical disease. In a third group, the tubular metabolic diseases, the primary defect is in the chemical organization of the tubular cytoplasm, presumably on a congenital basis. This is revealed in an isolated inability, of varying quantitative degree, to manufacture ammonia,[60] or to reabsorb amino-acids, phosphate or glucose adequately.[61] A remarkable type of disturbance is seen in a small percentage of patients with advanced nephritis whose tubules fail to reabsorb sodium to a degree comparable with the situation in severe adrenal cortical insufficiency.[62, 63] However, in the nephritic

cases, adrenal hormones are ineffective and the only effective treatment is a high intake of sodium chloride to compensate for the continued loss.

We shall learn much in the near future from modern renal physiological studies on patients with various tubular disturbances of hormonal or renal metabolic nature. The diagnosis of mild diabetes insipidus can be difficult but is readily made with the procedure of Hickey and Hare [64] in which the ability of the patient's hypothalamic-pituitary mechanism to respond to intravenous hypertonic salt solution is measured grossly by the effect on urine volume, and, in a more refined manner, by the change in concentration ratio of chloride in the tubular reabsorbate (R) to the chloride in the plasma (P). In the normal person, hypertonic salt solution (2.5 per cent) intravenously calls forth an increased secretion of pituitrin which sharply reduces the rate of urine flow and increases the chloride concentration in the urine because it increases the amount of water reabsorbed by the distal renal tubule. Hence the R/P ratio falls below one. In diabetes insipidus, the posterior pituitary cannot respond to hypertonic saline, the urine volume is not diminished, in fact increased by the extra salt, and the R/P ratio, which is above 1, does not change. This is a neat and objective test for the distinction of true diabetes insipidus from primary thirst and polydipsia.

For those who believe in the antagonism between pituitrin and adrenal cortical salt-retaining hormones as they act upon the renal tubule, opportunities to test the theory are afforded by unique clinical endocrine cases such as severe hypopituitarism, the Cushing syndrome and other conditions. Soffer's [65] salt and desoxycorticosterone test for adrenal cortical hyperfunction takes advantage of the altered renal response in a practical diagnostic test even though he has no adequate explanation for the results. We have already referred to the special behavior of the kidneys in essential hypertension toward sudden restriction of salt in the diet, or to the administration of Doca. These are only a few examples of the use of specific renal tubular functions in diagnosis and in the elucidation of pathological physiology.

Unfortunately, we still know next to nothing of the mechanism of renal diabetes or the other tubular metabolic or enzymatic disturbances of which the renin pressor and other vasoconstrictor activities [66] may be important consequences. However, the rapid progress of biochemistry of intermediary metabolism with the aid of isotopes should soon fill in many gaps in our knowledge of the kidney's tubular housekeeping, as it has done in the case of the liver.

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727 MENINGOCOCCIC CASES: AN ANALYSIS *

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Although an unusual amount of material in regard to meningococcic meningitis has been published since the introduction of the sulfonamides, and especially more recently following the discovery of penicillin, we believe our experience during the past few years is of more than ordinary interest.

From January 1, 1943, to December 31, 1946, there were 727 patients admitted to Municipal Contagious Disease Hospital with a diagnosis of meningococcic meningitis. The presence of meningitis accompanying meningococcemia might be questioned in 218 instances because no lumbar puncture was made, but in reality the clinical diagnosis was evident with few exceptions. There were 47 in which meningococcic infection was not confirmed by laboratory findings. Most patients who had no lumbar puncture did have either a positive blood culture for meningococci or a positive petechial smear. Ninety-seven per cent of our patients were treated without resort to either intrathecal therapy or spinal taps for drainage. The success attained by this plan is additional proof [1, 2, 3] that our method of therapy is justified.

March and April, as customary in this area, were the peak months of incidence; admissions for those months totalled 102 and 91 respectively for the four years (table 1). During the same period, September furnished the

Table I

Admission by Months

Month	1943	1944	1945	1946	Total
January	5	34	25	21	85
February	10	29	16	11	66
March	13	41	26	22	102
April	17	49	15	10	91
May	20	30	12	5	67
June	14	18	9	3	44
July	13	8	6	3	30
August	13	6	9	4	32
September	7	8	5	6	26
October	22	23	9	2	56
November	19	16	18	2	55
December	33	19	17	4	73
Total	186	281	167	93	727

smallest number of patients, which was only 26. Among all patients the ages ranged from seven weeks to 71 years. There were 39 infants less than a year of age, while on the other hand 127 patients were more than 35.

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From Municipal Contagious Disease Hospital, Chicago Health Department.

These age groups are of special importance because both are not usually included in reports coming either from children's hospitals or from military sources. Moreover, 315 or 43.3 per cent were females, a group not ordinarily found in the latter classification. Sex did not seem to be an important factor in respect to susceptibility at any age. In table 2 the cases are ar-

TABLE II

Patients According to Age and Sex

Year	0–1		1–5		6–10		11–25		26–35		36–45		46–65		66 plus		Total
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	
1943	5	11	24	21	7	12	27	23	10	7	11	10	7	11	0	0	186
1944	8	6	52	26	15	14	51	30	21	13	10	9	7	16	2	1	281
1945	6	1	32	14	8	4	34	19	9	10	9	8	7	3	1	2	167
1946	1	1	20	14	5	6	12	14	3	4	4	1	3	4	1	0	93
Totals by Sex	20	19	128	75	35	36	124	86	43	34	34	28	24	34	4	3	727
Totals by Age	39		203		71		210		77		62		58		7		727

Total Males.....412
Total Females.....315

ranged according to age and sex. All but 82 were white. There were 74 Negroes, 5 Mexicans, 2 Japanese, and 1 Philippino.

The average day of illness at time of admission was 3.1. But as it became generally known that meningitis was prevalent, the diagnosis was made more promptly in the third and fourth years than it was in the first two. This seems apparent because in 1943 the average day of illness from the onset until hospitalization was 3.7 for 186 patients, whereas in 1945 the corresponding average was 2.9 for 167 patients, and in 1946 it was 2.6 for 93 patients.

White blood counts were rarely excessively high, but ranged above 50,000 per cu. mm. in a few instances. The average leukocyte count for all patients was 17,360 per cu. mm. Blood cultures were positive in 51.4 per cent of 400. Among the 727 patients petechiae were present in 62.8 per cent, and for the latter blood cultures were positive in 42.7 per cent. Meningococci were found in smears from petechiae in the skin or mucous membranes of 153 patients, or 69.8 per cent of those examined. Because lumbar punctures were usually made only for the purpose of establishing a laboratory diagnosis, 41.8 per cent of the patients had no intrathecal tap after coming under our care; 29.9 per cent of all patients had no intrathecal tap either before or after admission (table 3). The average number of lumbar punctures for the entire series was less than one. Among the 423 patients whose spinal fluid was examined, smear or culture was positive for meningococci in nearly every instance (94 per cent). Spinal fluid cell counts averaged 11,491 polymorphonuclears per cu. mm.

TABLE III

Patients Who Had No Intrathecal Taps Either Before or After Admission

Year	0–1		1–5		6–10		11–25		26–35		36–45		46–65		Total		Total	Positive	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F		Blood Culture	Petechial Smear
1943			4	4	1		5	3	1				2	1	13	8	21	6	1
1944			26	9	5	7	16	7	5	1	4	4	1	4	57	32	89	40	47
1945	3		19	9	3	3	13	10	1	2	2	1	3	1	44	26	70	40	44
1946			11	10	2	1	6	3		1		1	1	2	20	18	38	23	28
Total	3		60	32	11	11	40	23	7	4	6	6	7	8	134	84	218	109	120

Typing of the organism was done in 241 instances. Of these 224 or 92.9 per cent were Type I. Nine patients suffered from Type IIa, seven from Type II, and there was but a single example of Type Ia. Inasmuch as Type I commonly predominates during most outbreaks of epidemic meningitis these figures are not surprising. All 17 patients not infected with Type I recovered. In view of the paucity of types other than Type I, the value of typing was not of major importance.

Two hundred ninety-eight or 40.9 per cent of the patients were comatose at the time of admission, and 74 or 10.1 per cent had one or more convulsions after hospitalization. There were only 28 or 3.8 per cent who showed evidence of opisthotonus and in nearly every instance where this occurred, it was present when the patient entered the hospital. This low figure is in sharp contrast to the frequency of opisthotonus during the days of intrathecal treatment with serum.

Diagnosis. Our routine procedure for hospital admissions consisted of a complete physical examination which included a white blood count, red blood count, and drawing of blood for culture. These procedures were carried out for every patient suspected of having meningitis, regardless of any special evidence in respect to the causative organism. In most cases smears were made from petechiae if the latter were present. All these routine measures were performed in the examining room before the patient was assigned to an isolation room or hospital ward.

The manner in which the diagnosis was established has been referred to. Nevertheless, we believe it is interesting to mention some of the conditions we were called upon to differentiate in the examining room. Approximately 41 per cent of all patients diagnosed as "suspect meningitis" prior to admission were found to be suffering from other conditions which included the following: brain tumor or abscess, spinal cord tumor, subarachnoid hemorrhage, poliomyelitis, epilepsy, tetanus, delirium tremens, and hysteria. Some with respiratory conditions which had been erroneously diagnosed as meningitis actually had such infections as tonsillitis, pharyngitis, sinusitis, various types of pneumonia, and in two instances foreign bodies in the

bronchi. Others with pertussis, scarlet fever, or German measles were also thought to have meningitis before entering the hospital. On a few occasions gastrointestinal conditions had been confused. Children were sent to us with intussusception, intestinal obstruction, gastroenteritis, or dysentery. Cardiovascular diseases gave cause for meningitis to be suspected. Acute rheumatic fever, subacute bacterial endocarditis, and valvular heart disease were sources for confusion. Chronic diseases were a basis for error in some cases where the patient was actually in diabetic coma, had diabetes and bronchopneumonia, chronic nephritis or uremia. Even dermatological conditions led to mistakes in the original diagnosis because dermatitis medicamentosa, erythema multiforme bullosa, papulonecrotic tuberculides, urticaria, and minute points of telangiectasis had evidently been regarded as skin manifestations of epidemic meningitis. Two men with typhoid fever and three with malaria had also been considered as possible cases of meningitis and were sent to the hospital for that reason. On the other hand, a number of patients who were reported as poliomyelitis, Von Economo's encephalitis, measles or chickenpox, were found after hospitalization to be suffering from meningococcic infection.

Complications. Exclusive of reactions which may be attributed to drugs, 23.3 per cent of all patients suffered from complications. There were 170 such patients. Arthritis was observed most commonly and occurred in 70 instances or 9.6 per cent. Deafness and panophthalmitis, fairly frequent in the days of intrathecal treatment, were comparatively rare in our series. In eight cases deafness was complete, occasionally being noted early in the course of the illness, but more often late. However, the disclosure could not always be made at the time of admission because some patients were comatose on arrival. There were eight additional instances in which deafness was partial, and in all of them improvement in hearing was either observed or anticipated at a future time. On the other hand, our experience has been that when hearing is entirely lost it is seldom regained. Panophthalmitis occurred twice and was present in both patients at the time of hospitalization. Hydrocephalus was a rare complication, and its presence determined only twice. These patients were infants, one two months and the other three and one-half months; both had hydrocephalus to a marked degree when admitted. Twenty patients had pulmonary involvement and all but four of these had bronchopneumonia. Among the 20 there were 12 deaths. There were also 12 others with terminal bronchopneumonia which was disclosed at autopsy. An unusual complication with recovery was pericarditis and effusion, generally a fatal occurrence. Another complication was facial paralysis which was noted eight times. Although a paralysis of this nature in acute infectious disease patients is rather frequently associated with a suppurative otitis media, none of these eight patients showed evidence of ear involvement; therefore, the condition may be explained on the basis of a toxic neuritis. None of the eight patients recovered the full use of

their facial muscles while in the hospital. One patient had a flaccid paralysis of an arm, another had a wrist drop, and a third a hemiplegia. Strabismus was present in 13 instances and otitis media in 12. Four patients had diplopia, 11 had conjunctivitis, and six had endophthalmitis. In none of these with ocular involvement was there complete loss of vision.

Treatment—Sulfonamide. No criterion was adopted for the selection of a sulfonamide. But an effort was made to use a fair diversity of the several drugs among the patients. The number treated with sulfadiazine and sulfathiazole was almost exactly the same. The small group given sulfamerazine may be explained by the fact that this drug was not available at all times. And long before the period had elapsed during which our series was completed, it seemed apparent that sulfapyridine did not approach in efficiency the other drugs that were employed. Nevertheless, all four groups seem to provide some suitable figures for comparison.

Irrespective of the drug used, the general plan of dosage was the same. In nearly all cases the initial dose of the medicament was by vein, and thereafter the sulfonamide was given orally when possible. Only in comatose patients was the intravenous injection repeated. In a comparatively small number, sulfonamides were administered subcutaneously. In determining dosage the weight of the patient was not given primary consideration, as commonly advised, but rather the seriousness of the illness and its duration. The initial dose for adults generally varied from 5 to 7 grams, and thereafter from 2 to 1 grams at four hour periods for all drugs with the exception of sulfamerazine with which the intervals were from six to eight hours. The average initial dose for children irrespective of age ranged from 3 to 5 grams which was followed by 1 gram every four hours. However, for infants the maximum initial dose rarely exceeded 2 grams which was nevertheless followed by 1 gram doses at four hour intervals. The average initial dose for all patients in our series, regardless of the drug, was 3.8 grams. The average varied from 4.1 grams for 186 patients treated in 1943 to 3.5 grams for 167 treated in 1945. For intravenous injection a 5 per cent solution of the sodium salt of the drug in normal saline was given, but for subcutaneous treatment the same preparation was employed in a 2.5 per cent solution.

The total average amounts of the drug per patient were: sulfadiazine 41.2 grams; sulfathiazole, 41.4; sulfapyridine, 41.0, and sulfamerazine 29.2 grams. Because there is such a sharp difference between the average amounts of sulfamerazine and the other drugs we believe that the larger doses used for sulfadiazine, sulfathiazole, and sulfapyridine are not essential for successful treatment. Although an effort was made to provide an adequate amount of fluids for each patient, the same degree of importance was not attached to administration of alkalies as a requirement. The average amount of parenteral fluid during the period of sulfonamide therapy was 3,728 c.c., and were it not for the fact that an abundant amount of fluids was given orally, the fluid intake for patients would appear to be low. We

usually prescribed from 2,000 to 3,000 c.c. of fluid for each 24 hour period with the exception of infants where the quantity was reduced in proportion to their size. One or more of the following fluids was customarily given parenterally: 5 or 10 per cent glucose in either saline or distilled water, 5 per cent glucose in Ringer's, Hartman's solution or M/6 sodium lactate.

Sulfonamide Blood Levels. Mention has been made that regardless of the drug selected there was practically no variation in dosage. Consequently, it has seemed particularly interesting to note the average levels for the different drugs. In every case a blood level was determined the day after patient's admission, and therefore the first blood level was secured within 12 to 24 hours following the initial dose of the drug. As a rule, several additional blood levels were obtained. The number of samples of blood for this purpose was based upon the response or lack of response to treatment or because of some drug reaction.

TABLE IV

Blood Levels and Fatality Rates According to Drug

Sulfonamide	Cases	Primary Blood Level	Average Blood Level	Deaths	Fatality Per Cent
Sulfadiazine	264	20.7	18.9	37	14.0
Sulfathiazole	263	7.7	7.1	34	12.8
Sulfamerazine	127	16.4	14.7	17	13.3
Sulfapyridine	68	13.9	10.7	17	25.0

In table 4 the primary levels for the various drugs and the average of all levels for each drug are shown. It appears that the highest blood levels after the initial dose, 20.7 mg. per cent, were obtained with sulfadiazine. Moreover, when the average of all levels was computed it was found that sulfadiazine with 18.9 mg. per cent was considerably higher than any of the corresponding levels for the other drugs which were: 14.7 for sulfamerazine, 10.7 for sulfapyridine, and 7.1 for sulfathiazole. It is especially noteworthy that both the primary and also the averages of all levels were lowest with sulfathiazole. However, with sulfathiazole the figures for the primary levels and the average level showed a smaller degree of difference than occurred between the primary levels for any of the other drugs.

Based on the figures presented in table 4 it seems proper to infer that the importance attached to sulfonamide blood levels has been overemphasized. It also seems likely that in the case of the drugs used dosages were much higher than may be required for satisfactory treatment. The first statement in this paragraph is really more than an inference because the fatality rates in our series for sulfadiazine, sulfamerazine, and sulfathiazole were practically the same (table 4). This was true, notwithstanding that the average of all blood levels for sulfadiazine was more than two and one-half times the corresponding average for sulfathiazole. And the average of all blood levels for sulfamerazine was more than twice the corresponding average for sulfa-

thiazole. Our figures suggest that high blood levels may not be an essential requirement for the efficient treatment of meningococcic meningitis. Furthermore, since low blood levels mean still lower spinal fluid levels, it seems apparent that the amount of the drug which enters the cerebrospinal fluid circulation is not necessarily a determining factor in the recovery of the patient.

Average Number of Days on the Sulfonamides. Although there was no prearranged plan in regard to any definite number of days for therapy, we find, irrespective of the sulfonamide employed, that the average length of time in 1943 and 1944 was almost identical; the figures were 8.7 and 8.9 days. But in 1945 many patients received the drug for a shorter period and the average time was 7.5; this was reduced still further to only 6.7 days for the year 1946. As a consequence the average duration of sulfonamide medication for our entire series was 8.3 days, but we found that in many instances five days' treatment was sufficient. All of these averages refer to recovered patients.

From the standpoint of economy of time on the part of patients and also the availability of beds and cost of care, the period of hospitalization deserves important consideration. Notwithstanding that we have been overcautious in regard to releasing patients until we felt that they had completely recovered from their illness, the average duration of hospitalization for all recovered patients was only 11.5 days. For the 150 recoveries in 1943 the average lapse between admission and discharge was 13.3 days, whereas in 1946 the corresponding average was reduced to 9.8 days. These figures are scarcely more than half as great as some that have been published.[4] Moreover, they are in sharp contrast to the time when intrathecal serum was in vogue and three to five weeks' hospitalization[5] was not unusual. The minimum isolation period for meningococcic meningitis in Illinois is one week from the date of onset.

TABLE V

Hematuria with Different Drugs

Drug	Cases	Hematuria	Per Cent
Sulfadiazine	264	154	58.3
Sulfapyridine	68	28	41.1
Sulfamerazine	127	44	34.6
Sulfathiazole	263	53	20.1
Total	722	279	38.6

Complications Associated with Sulfonamide Treatment. In table 5 drugs are indicated together with the number of patients who developed hematuria including microscopic as well as gross blood. The percentage of those who had hematuria with the different drugs is also shown. It may be seen that sulfadiazine was chiefly responsible for this condition. Moreover,

it is strikingly apparent that sulfathiazole was less often the offender than any of the others. The high percentage (58.3) for hematuria with sulfadiazine follows closely our past experience.[6] In addition the low figure (20.1 per cent) for patients treated with sulfathiazole is also in conformity with former observations.[6] There was a single fatality resulting from anuria and this occurred in the sulfadiazine group. We implied previously that the value of giving an alkali when using sulfonamide drugs is probably not of as great importance as the administration of adequate amounts of fluid. Our basis for this view is that 58.2 per cent of the patients received alkali, usually soda bicarbonate, in doses equal to or more than the amount of drug administered, and yet there was no significant difference in hematuria frequency for the group that had an alkali and the group that did not.

Herpes simplex occurred in approximately 8 per cent of our patients. However, in nearly all cases it did not develop until after several days' administration of sulfonamides and therefore was attributed to a drug reaction in most cases. Maculo-papular eruptions associated with conjunctivitis were noted in a few instances, the most severe ones being in the sulfamerazine treated group. Several patients had an erythema nodosum during sulfathiazole or sulfadiazine therapy. In infants and small children a hyperpyrexia was occasionally observed late in the course of sulfonamide administration and subsided upon cessation of the drug. Unless reactions were of unusual severity or manifest late in the course of treatment, sulfonamide therapy was not discontinued. Sometimes sulfanilamide was substituted when hematuria was present.

Penicillin Therapy. Among 727 patients there were 103 or a little more than 14 per cent who were treated with penicillin as well as one of the sulfonamides. Two patients received penicillin exclusively. In this group of 103 there were 27 deaths or a fatality rate of 26.2 per cent, indicating a death rate for the penicillin treated patients which was nearly three times greater than for those who received no penicillin. Among the 27 penicillin fatalities, nine received the drug intrathecally and two intravenously as well. Of the two patients given penicillin exclusively, one was treated by the intramuscular route and recovered, and the other received the drug entirely by vein and died. Both of these cases were meningococcemias rather than meningitis. Table 6 shows the number of patients who were given penicillin and a sulfonamide in combination and the outcome.

Our experience with penicillin for meningococcic infections has been disappointing. Because of the poor results secured with intrathecal administration [7] this route was soon abandoned. Furthermore, we observed instances where as much as 600,000 units were injected intravenously within the first 24 hours of illness without any apparent effectiveness. In some cases penicillin was given alone at the customary three hour intervals in from 15,000 to 40,000 unit doses over a period of from five to six days without clinical improvement in the patient's condition. We were not convinced

TABLE VI

103 Patients Treated with Both Penicillin and Sulfa Drug

Year		0–1		1–5		6–10		11–25		26–35		36–45		46–65		Recoveries		Deaths	
		M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
1944	Rec.			1	2				1	2	2					3	5		
	Died		1					1		3					1			4	2
1945	Rec.	4		8	5	3	2	4	5	3	3	1	3	2		25	18		
	Died	2		3	1			2		1	1	2		2				12	2
1946	Rec.			4	7	1	3	2	3		2	2		1		9	16		
	Died			2				3				1		1				7	
	Total	6	1	18	15	4	5	12	9	9	8	6	3	6	1	37	39	23	4

that patients treated with both a sulfonamide and penicillin responded more rapidly than patients treated only with a sulfonamide. Notwithstanding our unfavorable views in regard to the value of penicillin for the general treatment of meningococcic meningitis, we believed that it was strikingly helpful for eye [8] complications, but the opportunities for estimating its worth in such conditions were limited.

General Treatment. Regardless of the severity of the infection, we did not use either anti-bacterial serum or antitoxin.[9] But for patients who showed evidence of shock or presented the customary picture of the Waterhouse-Friderichsen syndrome, adrenal cortical extract was injected. Generally the intramuscular route was adopted but we believe that some patients would have benefited to a greater degree if the intravenous route had been selected.[10]

The need for administration of sedatives, particularly morphine, in connection with the treatment of meningitis is often considered. In most of our cases no sedatives were prescribed. However, when patients were irrational one of the following drugs was sometimes used: phenobarbital, sodium amytal, seconal chloral hydrate, sodium bromide, or paraldehyde. For those who were very difficult to control we found paraldehyde to be of particular value. Contrary to the opinion sometimes expressed, we believe that morphine should not be used for meningitis. Our opposition to the last named drug is based on personal observations. There seems to be no doubt that morphine may produce or increase edema of the brain as well as depress the respiratory center. Progress toward recovery appeared to be retarded in those patients who received morphine prior to hospitalization. In every case bed restraints should always be applied during the acute stage of the disease.

Prognosis and Fatality Rates. Age is always considered one of the im-

portant factors in prognosis and this is shown to be true in our series, for those in the two extremes of life suffered the greatest casualties. Prognosis was most favorable in the groups from six to 10 years of age and among those from 11 to 25 as exhibited in table 7.

TABLE VII

Fatality Rates by Age

Age	Cases	Deaths			Fatality Per Cent
		24 hour	48 hour	Total	
0–1	39	5	2	11	35.4
1–5	203	18	4	24	11.7
6–10	71	2	0	2	2.8
11–25	210	8	4	19	9.0
26–35	77	2	4	11	14.2
36–45	62	4	3	16	24.5
46–65	58	7	2	21	36.2
65+	7	1	1	4	57.1
Total	727	47	20	108	14.8

Excluding 24 hour deaths—Fatality rate 8.9 per cent.
Excluding 48 hour deaths—Fatality rate 6.2 per cent.

Race seemed to play an insignificant part in prognosis. There were 645 white patients with a fatality rate of 14.8 per cent. Among 74 Negroes there were 10 deaths, or 13.5 per cent. There were also five Mexicans with one death, two Japanese who recovered, and one Philippino who failed to survive. Irrespective of race, the attack rate was higher for the males. Fifty-six and eight tenths per cent of the white patients were males, and 43.1 per cent were females. For Negroes 58.1 per cent were males and 41.8 per cent females. However, in both races the chances for recovery were slightly in favor of females, the fatality figures being as follows: white males 15.2 per cent; white females 14.3 per cent; Negro males 13.9 per cent; Negro females 12.9 per cent.

Patients entering the hospital in coma or suffering from convulsions were usually regarded as having a doubtful prognosis. This observation is not an uncommon one. Those with high temperature at the onset often responded better to sulfonamide therapy than the ones who had little fever. Possibly a marked pyrexia indicated to some extent the patient's degree of resistance.

Among all 727 patients there were 108 deaths or a fatality rate of 14.8 per cent. However, 67 died within 48 hours of admission, and included in the latter group were 47 where death occurred within less than 24 hours from the time of hospitalization. If these 47 were excluded the corrected fatality rate for 680 patients would be 8.9 per cent. With deduction of the 48 hour deaths which included all moribund cases, the fatality rate for 660 patients is 6.2 per cent.

Seventy-seven autopsies were performed and among these lobar or bronchopneumonia was present in 22 instances, as well as the customary intracranial findings. In 11 cases the Waterhouse-Friderichsen syndrome was confirmed at necropsy. As may be noted in table 4, the percentage of fatalities did not vary significantly regardless of the sulfonamide that had been used for treatment.

We were impressed by the fact that on a number of occasions in which the clinical diagnosis was strongly indicative of Waterhouse-Friderichsen syndrome, autopsy disclosed no gross or microscopic pathological changes in the adrenal glands. This may explain some of the reported recoveries in which the Waterhouse-Friderichsen syndrome was diagnosed.

Summary

Among 727 meningococcic patients ranging in age from seven weeks to 71 years, there were 108 deaths, or a fatality rate of 14.8 per cent. Sixty-seven of the patients were moribund when admitted, and among these there was pathological or clinical evidence of the Waterhouse-Friderichsen syndrome in 20 instances. If all moribund patients are excluded, the fatality rate is 6.2 per cent.

A large number of the patients had meningococcemia and nearly all showed evidence of meningitis; 62.8 per cent had petechiae, and 69.8 per cent of the petechial smears were positive for meningococci. Fifty-one and four tenths per cent of blood cultures were also positive for meningococci. Among the 423 patients who had an intrathecal tap as a diagnostic measure, the spinal fluid smear or culture was positive for meningococci in 94 per cent. There were 47 patients in whom an absolute diagnosis was not confirmed by laboratory procedures, although clinically most of these were examples of meningococcemia and some had received treatment before hospitalization.

When the clinical diagnosis was confirmed by petechial smear or positive blood culture an intrathecal tap was not considered necessary; as a consequence, the entire group of 727 patients had an average of less (0.7) than one lumbar puncture; 41.8 per cent of the patients had no lumbar puncture after admission. There were 218 or 29.9 per cent who had no spinal tap either before or after hospitalization.

Only 22 patients received intrathecal therapy, the remedy used being penicillin, and the fatality rate for this group was 40.9 per cent. They also received a sulfonamide.

There was but slight difference in therapeutic efficiency regardless of the sulfonamide drug that was administered. However, the actual percentage of recoveries was highest for the patients who were treated with sulfathiazole. Fatality rates for the several drugs were as follows (table 4): sulfadiazine 14 per cent; sulfathiazole 12.8 per cent; sulfamerazine 13.3 per cent, and sulfapyridine 25 per cent.

The average number of days ill prior to admission was 3.1 and the average number of days on sulfonamide therapy was 8.3. The length of stay in hospital for recovered patients averaged 11.5 days. In spite of the short period of hospitalization there was not a single instance of a relapse or recurrence [11] following release from isolation.

COMMENT

We feel that our results in the treatment of *727* patients with meningococcic infections are a conclusive demonstration that intrathecal therapy is not necessary for meningitis. Moreover, we have also shown that frequent lumbar punctures for drainage are not required. In our opinion, penicillin is not a valuable adjunct in the treatment of meningococcic infections but is an efficient aid in the management of eye complications. We have shown also that the sulfonamide blood level is not always a reliable guide for determining the effectiveness of the drug. Although sulfathiazole levels are low, there is no doubt in regard to this drug's usefulness [12] for the treatment of meningococcic meningitis. Therefore we question the emphasis which is customarily placed on the value of blood levels when considering prognosis.

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SPECULATIONS AS TO THE THERAPEUTIC SIGNIFICANCE OF THE PENICILLIN BLOOD LEVEL*

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I. THE DIRECT BACTERICIDAL ACTION OF PENICILLIN

PENICILLIN is actively bactericidal in vitro [1, 2, 3, 4, 5, 6, 7]; and although the body's cellular or humoral defense mechanisms probably play a contributory rôle in vivo, that direct bactericidal action may be largely responsible for the therapeutic activity of the drug.

The susceptibility of a given organism to penicillin may be defined in terms of three concentrations (figures 1 and 2; cf. also [2, 6, 7]). The first is that which suffices only to reduce the normal rate of multiplication, and is illustrated by curve 0.004 in figure 1 and point A in figure 2. At a somewhat higher concentration (e.g. curves 0.006 and 0.008 in that figure and point B in figure 2), the organisms are killed faster than they multiply, so that there is a progressive, slow decrease in the number of viable organisms.† This minimally effective level approximates the "sensitivity" of the organism to penicillin as ordinarily defined, i.e., the concentration at which the organism fails to grow out visibly in culture. It does not, however, represent the most effective concentration of the drug. Even a slight increase in penicillin beyond this minimally effective level causes a striking increase in the rate at which the organisms are killed by penicillin. One soon, however, attains a concentration of penicillin at which the organisms are killed at a maximal rate (point C in figure 2, and curve 0.064 in figure 1). This maximally effective level of penicillin usually varies between two and 10 times the concentration which barely suffices to reduce the number of viable organisms (table 1); and even a 10,000-fold increase beyond this optimal level does not further increase the rate at which the organisms can be killed by penicillin.

It is a reasonable surmise that the concentration of penicillin which is maximally effective in vitro indicates the approximate level which should be maintained at the focus of infection in vivo in order to kill the largest number of organisms in the shortest possible time. Coupled with information as to the distribution of penicillin between the blood and tissues, it may then be possible to use the penicillin plasma level as a guide to the most ef-

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† With some organisms, at threshold concentrations of penicillin one often observes an initial net bactericidal effect, followed in six, 12, 24 or even 48 hours by their rapid multiplication, often to a degree exceeding that in a control culture. This secondary growth is not primarily due to the deterioration of penicillin, and will be discussed more fully in a following paper.

fective therapeutic use of penicillin. If the penicillin concentration is less than optimal during a large portion of the treatment period, then the time necessary to effect cure may be unnecessarily prolonged. On the other hand, excessively high concentrations serve no useful purpose as such, unless they can be shown to promote the body's own defense processes. The sole advantage of extremely large doses of penicillin may consist in the fact that

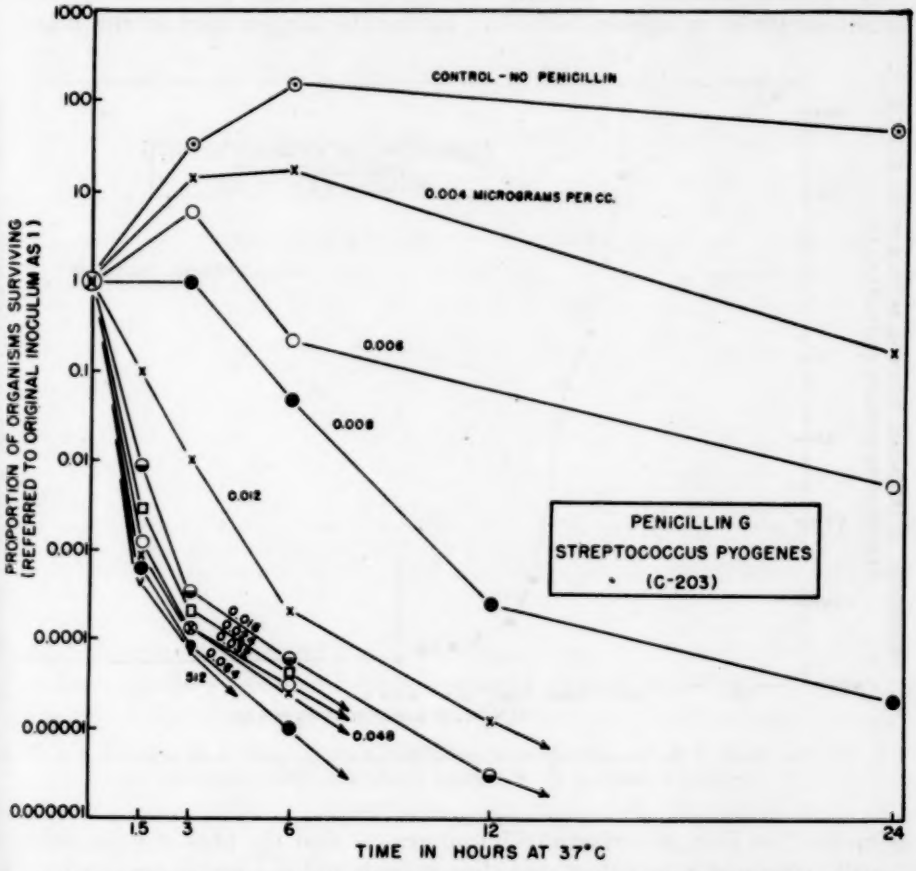

FIG. 1. The effect of the concentration of penicillin on the rate at which streptococci (C-203 strain of *Streptococcus pyogenes*) are killed in vitro (from Eagle and Musselman[28]).

they provide the maximally effective concentration for longer periods of time. Indeed, with some strains of streptococci and staphylococci, there is a rather sharply defined optimum concentration of penicillin in excess of which these organisms are killed at a paradoxically slower rate.[8] If this should prove to be the case also in vivo, then with these particular organisms, excessively large doses might actually be less effective than either multiple small doses, or a continuous infusion which maintained the penicillin concentration in the tissues at approximately the optimally effective level.

II. Pharmacologic Considerations

A. *The Penicillin Concentration in the Blood, and the Error in Its Bioassay Caused by the Presence of Serum.*

At a given moment, the plasma level of penicillin is being modified by many different factors.

(1) *Absorption from the site of injection.* When penicillin is injected intramuscularly in aqueous solution, by far the largest part of the injected

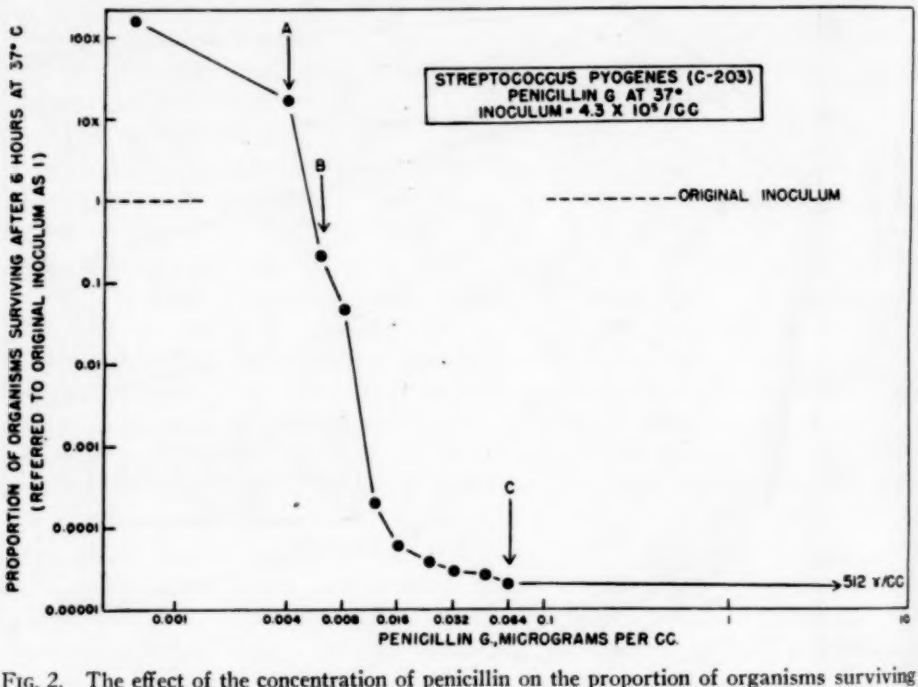

Fig. 2. The effect of the concentration of penicillin on the proportion of organisms surviving after 6 hours at 37° C. (from Eagle and Musselman [28]).

penicillin has been absorbed in 15 minutes, so that the peak concentration is usually obtained in less than that time period, and is roughly proportional to the amount injected (figure 3, from [9]). Absorption is, however, markedly delayed by injecting a suspension of penicillin in oil and beeswax.[10]

(2) *Rate of urinary excretion.* Amorphous penicillin, and crystalline penicillins F, G, and X, are excreted by the kidney at a rate which corresponds essentially to the total removal of penicillin from all the blood reaching that organ.[11] (The anomalous low renal clearance of penicillin K is a special case which is not relevant to the present discussion.) It is primarily in consequence of this rapid excretion that the blood levels of penicillin fall so rapidly after a single intramuscular injection of an aqueous solution (figure 3).

TABLE I

"Effective Levels" of Penicillin G for a Number of Bacteria (Eagle and Musselman[28])

Infecting organism	Concentration of penicillin G (micrograms per c.c.)[a] which sufficed to			Time required to kill 99.9 per cent of organisms at optimal concentrations of penicillin	Proportion of organisms surviving after 6 hours exposure to maximally effective concentrations of penicillin
	reduce rate of growth	slowly kill the organisms	kill the organisms at maximum rate		
Streptococcus pyogenes (C-203)	0.004	0.006–0.008	0.064	1.5–2 hrs.	0.002–0.004%
Pneumococci (Types 1, 3, 8, 12, 14, 24)	0.008–0.012	0.024	0.064	3–5 hrs.	0.03%±
Staphylococcus aureus (6 susceptible strains)	0.016–0.024	0.024–0.064	0.064–0.25	5–20 hrs.	0.05–1.0%
(1 resistant strain)	0.25	1	16	11 hrs.	6%
Treponema pallidum (Reiter)	0.016	0.032	1±	25–35 hrs.	5–10%
Streptococcus fecalis (5 susceptible strains)	1	2–4	4–6	5 hrs.	0.05%
(2 resistant strains)[b]	1	3–4	4–6	>48 hrs.	10–50%

[a] To transform to units, multiply by factor 1.7 (1 mg. = 1667 units).
[b] Resistant in that organisms were killed only slowly even at optimal concentrations of penicillin.

(3) *The inactivation of penicillins by plasma.* Penicillins F, G, and X have been shown to be slowly inactivated in plasma at 37° C. However, that inactivation proceeds so slowly as to be of negligible quantitative significance in comparison to the rate of renal excretion.

(4) *Diffusion of penicillin out of the blood into the tissues* continues as long as the concentration of diffusible penicillin in the plasma exceeds that in the tissues.

(5) *Diffusion of penicillin out of the tissues into the blood* begins as soon as the concentration of diffusible penicillin in the plasma falls below that in the particular tissue. Large injections may create a significant reservoir of penicillin in the body fluids and perhaps in the body cells; and the fact that, as is evident after large injections, the average plasma levels of penicillin fall off at a progressively slower rate may reflect the diffusion of penicillin back from this tissue reservoir into the blood (figure 3) (cf.[26, 30]).

(6) *The effect of serum on the bioassay of penicillin.* In the determination of the penicillin concentration in the serum or other body fluids, the measuring rod ordinarily used is the inhibitory effect of the specimen on the growth of a susceptible test organism. A significant error may be intro-

duced in such assays by the presence of the serum itself.[12, 13, 14, 15] Tompsett, Schultz and McDermott [15] have shown that when penicillin G is added to whole serum, approximately half the penicillin is bound to the serum protein, and thereby prevented from acting on the test organism; and in the case of penicillin K approximately 90 per cent is so bound. A quantitatively less important error is the partial inactivation of penicillin during the assay by the serum itself.[12, 13, 14] Fortunately, the amount of penicillin bound or inactivated, and thus, the magnitude of the serum error, is related to the serum concentration; and in methods of assay in which the test serum is serially

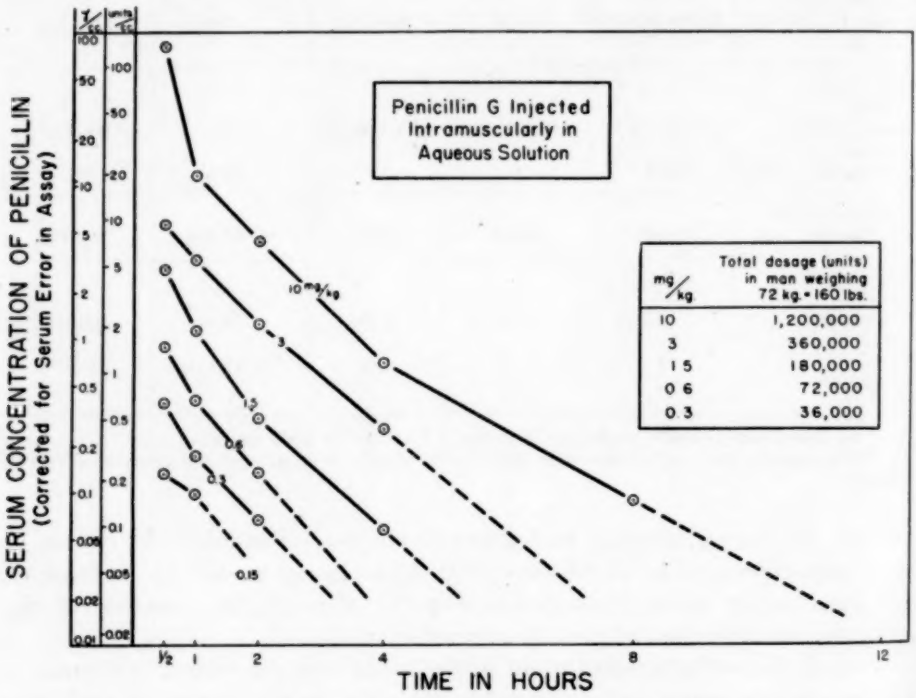

FIG. 3. The serum concentration of penicillin G in man after its intramuscular injection in aqueous solution.
Each value in the figure is the median of at least 10 patients (from Tucker and Eagle [9]).

diluted, the higher its penicillin content, and the higher the dilution which suffices to inhibit the growth of the test organism, the smaller is the serum error.

Thus, the bioassay technic used in this laboratory [11, 13] is a serial dilution technic in which the C–203 strain of *Streptococcus pyogenes* is the test organism, the production of hemolysis is the criterion of growth, and the highest dilution of the serum which just suffices to prevent hemolysis is a measure of its penicillin content.[16, 17] As just discussed, the magnitude of the error introduced by the presence of serum depends on the serum concentration in

the indicator tube, i.e., the particular dilution which just suffices to prevent hemolysis. This is shown for both penicillins G and K in table 2 and figure 4. Each point in that figure is the average of 8 to 11 determinations, with as many different human sera. In figure 5 the results have been expressed as the corrective factors by which the apparent penicillin content of the serum (based on the highest dilution which suffices to inhibit hemolysis) must be multiplied in order to correct for the inhibitory effect of serum in the assay.

TABLE II

The Effect of Human Serum on the Bioassay of Penicillin (after Eagle and Tucker[37])

Penicillin species	Concentration of serum in the penicillin assay, %	Apparent activity of penicillin, %		Corrective factor (based on means)
		mean	median	
G	96	35	38	2.9
	48	52	50	1.9
	24	73	67	1.4
	12	97	100	1.0
K	96	6	6	18.2
	48	14	13	7.4
	24	28	30	3.6
	12	50	50	2.0
	6	72	67	1.4

The data of figures 4 and 5 are clearly applicable only to the particular technic under discussion; but similar curves can be elaborated for any bioassay technic. Further, although these data were obtained with human sera, qualitatively and quantitatively similar results have been obtained with rabbit sera.

B. *The Concentration of Penicillin in the Tissues.*

The plasma penicillin concentration can be readily determined at any time during the therapeutic administration of the drug. However, it is the concentration at the focus of infection which is the important therapeutic consideration, and the plasma level is of significance only insofar as it provides a measure of that tissue concentration. Large differences can and do exist between the two, and individual organs vary widely in the magnitude of that differential,[18-23] In general, except for the spinal fluid, and walled-off, relatively avascular foci (e.g. organized thrombi, abscesses), the desired concentration of penicillin can be delivered to a focus of infection by maintaining between two and 10 times that concentration in the circulating plasma.

The most important factor affecting the plasma: tissue ratio of penicillin is probably its rate of diffusion from the blood into the particular organ. A second important factor is the fact that penicillin is reversibly bound by the serum proteins. With penicillin G, approximately half the penicillin is so bound,[15] so that the concentration of diffusible penicillin available for dis-

tribution to the tissues at any moment is therefore only half the total plasma concentration. Finally, the magnitude of the concentration differential between the plasma and a given tissue will be materially affected by the rate at which penicillin is locally inactivated by that particular tissue.[23, 24, 25] Although there are as yet no supporting experimental data, it is possible that penicillin may be not only inactivated, but also reversibly bound by the tissues. Under such circumstances the slow dissociation of penicillin from its com-

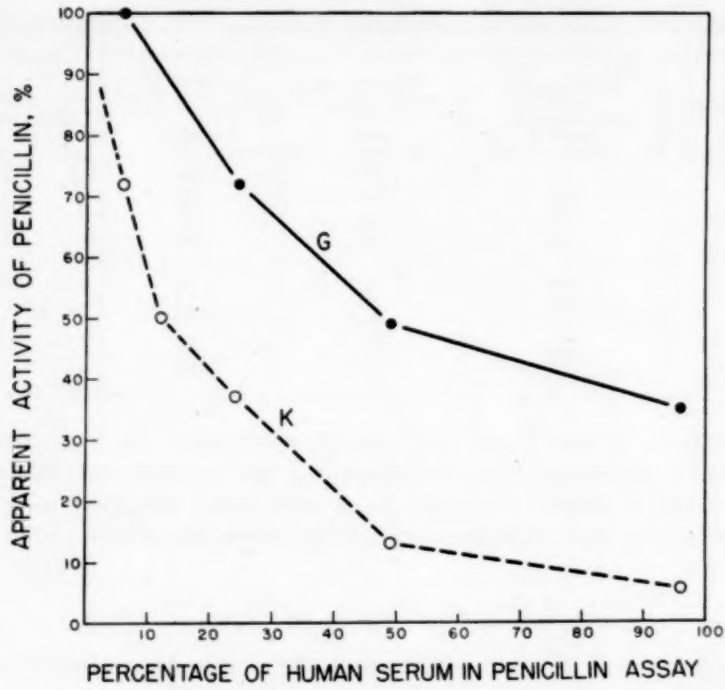

FIG. 4. The inhibitory effect of human serum on the bioassay of penicillin, with C-203 *Streptococcus pyogenes* as the test organism (from Eagle and Tucker [37]).
Each point in the figure is the average of 8 to 11 determinations with as many different sera, as indicated in table 2.

bination with the tissues after it had largely disappeared from the blood might make it active locally for a much longer period than would be implied by the blood level curves.[26, 30, 35, 38]

III. Duration of the Therapeutic Effect of a Penicillin Injection [26, 31, 35, 38]

The tissue penicillin levels after the intramuscular injection of penicillin in aqueous solution, and the therapeutic (bactericidal) activity of those levels, may be indicated diagrammatically as in figure 6. If concentration level A in that figure is that which kills a given organism at the maximal possible

rate, and B is the lowest concentration which, although not maximally effective, nevertheless does have a net bactericidal action in vitro, then the therapeutic efficacy of the injection may be measured in terms of three time periods, as indicated by the horizontal line at the bottom of that figure:

(1) The time for which the injection provides concentrations at the focus of infection equal to, or in excess of,* the maximally effective level A, and during which the organisms are being killed at the fastest possible rate.

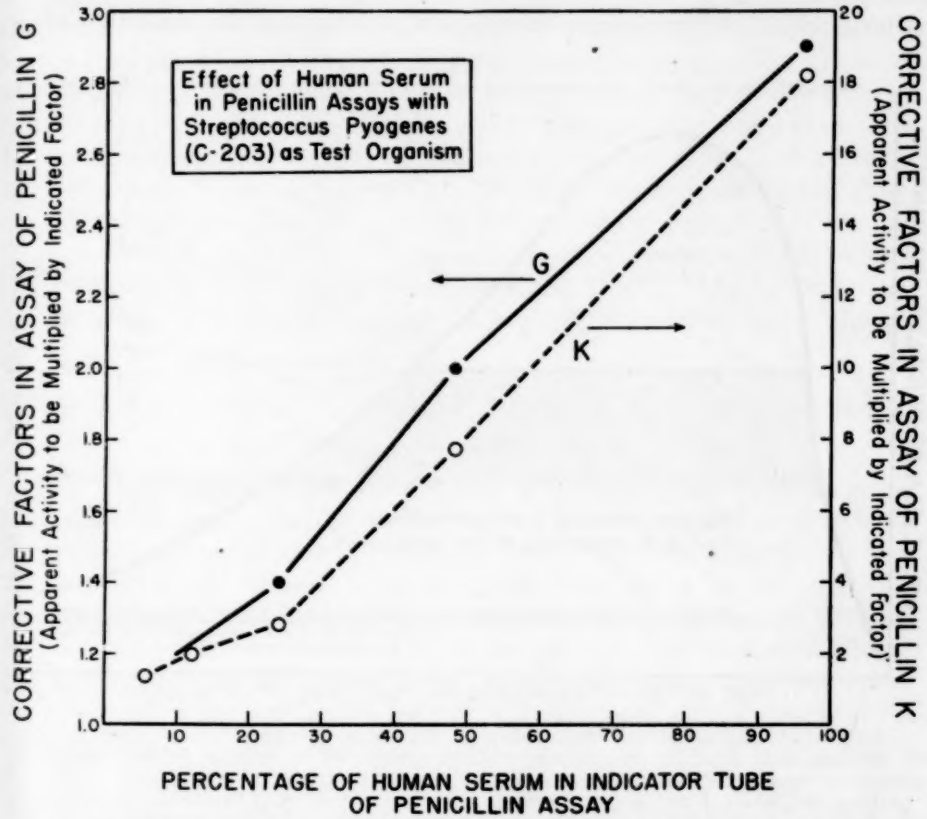

FIG. 5. Corrective factors in the bioassay of penicillins G and K (after table 2) (from Eagle and Tucker [37]).

Abscissae are the concentrations of serum in the dilution which just suffices to inhibit hemolysis, and thus serves as the indicator of its penicillin content. Ordinates are the corrective factors by which that apparent penicillin activity must be multiplied in order to correct for the inhibitory effect of that concentration of serum on penicillin activity.

(2) The time for which the penicillin concentration is at effectively bactericidal concentrations, intermediate between the maximally effective level A and the minimally effective level B.

* This will not be true for organisms with a sharply defined optimal zone of penicillin concentration. For such bacteria, concentrations in excess of A are paradoxically less effective, and the time for which the concentration is in excess of that value is not a measure of the total therapeutic effect.

(3) Recovery period. Parker [32] has shown that when organisms are exposed to penicillin in vitro, the survivors do not begin to multiply as soon as the drug is removed. Instead, there is a definite recovery period before the surviving organisms begin to multiply to a significant degree. In vivo also, the experiments of Jawetz [26] indicate that in infected mice treated with penicillin, the number of surviving viable bacteria continues to fall for some time after the serum penicillin has fallen to concentrations far below those which are effective in vitro. Whether this continuing disappearance of bacteria reflects the persistence of penicillin in the tissues for some time after

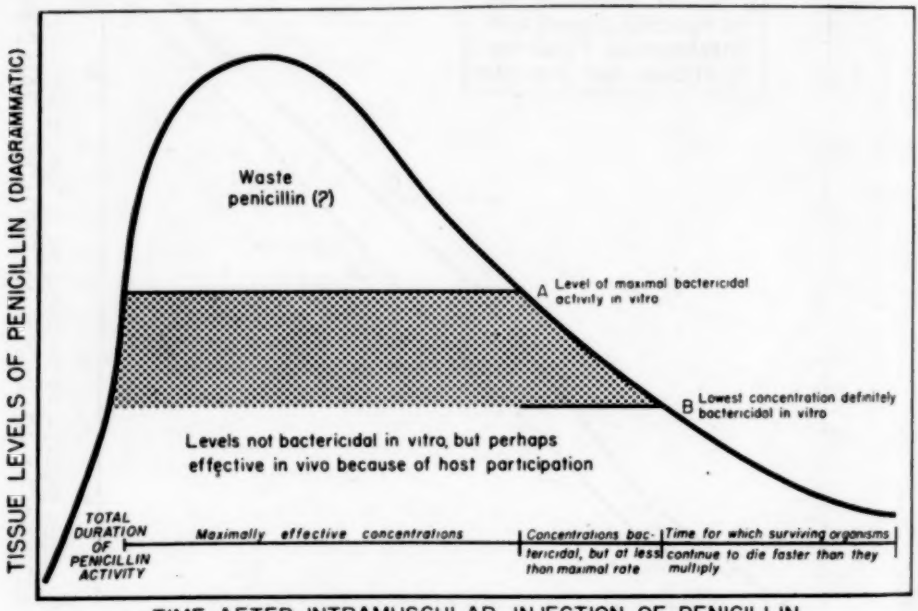

FIG. 6. A diagrammatic representation of the tissue concentrations of penicillin after its intramuscular injection in aqueous solution, considered in relation to the bactericidal activity of these concentrations.

Penicillin levels A and B correspond to those in figure 2: A is that which is maximally effective in vitro, and B is the smallest concentration which effects a net reduction in vitro in the number of viable organisms.

it has disappeared from the serum (cf. page 263); whether organisms exposed to penicillin may die as the result of that exposure long after the penicillin has disappeared from the surrounding fluid; or whether bacteria exposed to minimal concentrations of penicillin are thereby rendered more vulnerable to the body's normal defense mechanisms, so that concentrations ineffective in vitro may nevertheless be effective in vivo, are points for further study.[26]

In summary, the activity of penicillin is probably determined by a composite of three time periods: the time for which it is at maximally effective concentrations; the time for which it is at concentrations which have a defi-

nite if slower bactericidal action; and the as yet indeterminate but quantitatively significant period, after penicillin has fallen to levels not bactericidal in vitro, during which some of the bacteria continue to die at a faster rate than the other reviving survivors can multiply.

One final point cannot here be considered in detail, but is relevant to this present discussion. With organisms which are killed most rapidly at a narrow optimum zone of penicillin concentration,[8] and which die only slowly at concentrations in excess of this optimum level, aqueous injections of penicillin may be an inefficient method of treatment, since the optimally effective level is then provided for a relatively short time. Such organisms are killed only slowly while the penicillin is present in large excess; the rate of killing increases rapidly as the tissue concentrations approach the range of optimal concentration; and the rate falls off again as the concentration falls below the effective level. With such organisms, the most effective method of treatment may well be either (a) the administration of penicillin in oil and beeswax, or (b) a continuous intramuscular or intravenous infusion at a rate calculated to maintain the tissue concentrations at approximately that optimal level. The latter is technically more difficult, but susceptible of more precise control.

IV. Is It Necessary to Maintain the Blood and Tissue Concentration of Penicillin at Bactericidal Levels?

It is clear from the preceding paragraphs that the penicillin levels in the blood may temporarily fall below those which are bactericidal in vitro without prejudicing the outcome of treatment. It is, however, equally clear that this "penicillin-free" interval between injections cannot be unduly prolonged without permitting the regrowth of the surviving organisms to such a degree as to counteract the therapeutic effect of the preceding injection of penicillin. The maximum time for which penicillin may be permitted to fall below effective levels without affecting the outcome of treatment will vary with the recuperative power of the particular organism and its normal rate of multiplication. An instructive contrast in this respect is afforded by experimental infections with *T. pallidum* and *Diplococcus pneumoniae* type I (figures 7 and 8).

The division time of *T. pallidum* in rabbits has been estimated, on the basis of the varying incubation periods after inocula of varying size, to be on the order of 30 hours.[27] This is to be compared with an observed division time in vitro of 10 hours for the cultured Reiter strain of *T. pallidum*.[28] Corresponding to this slow rate of multiplication, when syphilitic rabbits were treated intramuscularly with 16 doses of penicillin in aqueous solution, it was found that it made only a slight difference in its therapeutic activity whether the material was administered every four hours, twice daily, or even daily.[29] The total curative doses on these three schedules were 4000 (approximately), 1770 and 4000 units/kg.; and a dose of 250 units/kg. per

injection cured 50, 100 and 57 per cent of the animals, respectively. Since the latter dosage of 250 units/kg. provided a measurable level (0.03 unit) in rabbits for significantly less than two hours, it follows that when it was given only once daily, for at least 20 hours out of the 24 * the blood and tissues

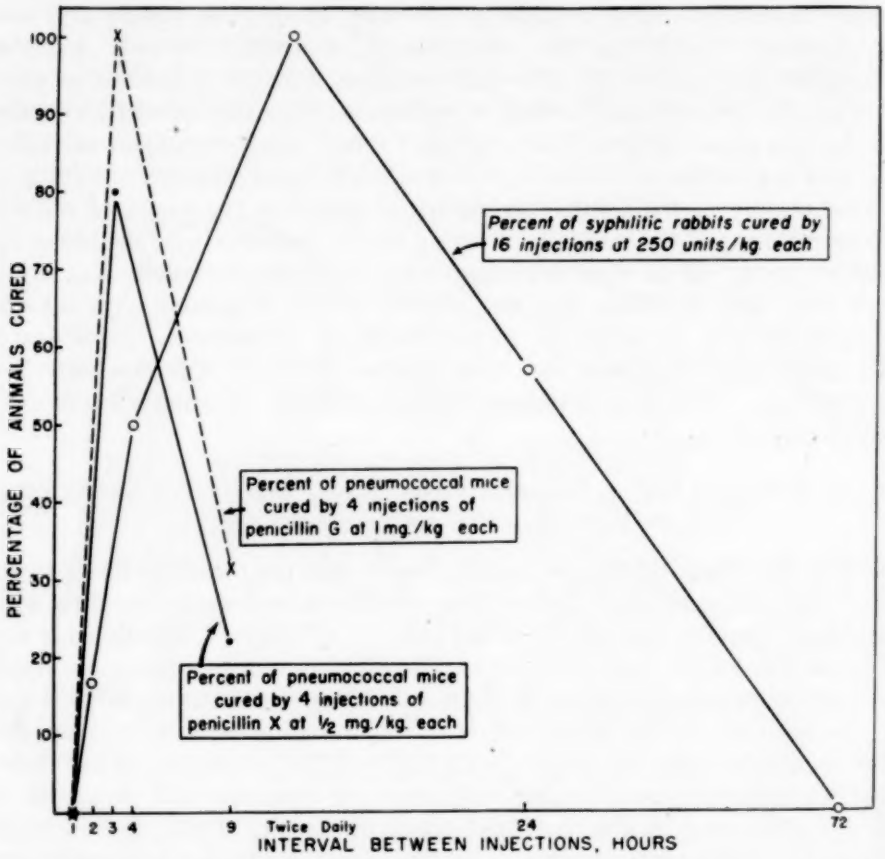

FIG. 7. The effect of the interval between injections on the therapeutic efficacy of a given dose of penicillin.

In pneumococcal infections of white mice, penicillins G or X administered at 9-hour intervals were far less effective than the same dosages administered at 3-hour intervals, due to the rapid re-multiplication of survivors in the penicillin-free interval. In the case of syphilitic infection, however, and reflecting the slow multiplication of the organisms, the interval between injections could be prolonged to 24 hours without abolishing the therapeutic efficacy of the drug. With even longer time intervals between injections, however, the organisms multiplied sufficiently in the penicillin-free interval to counteract the effect of the preceding injection.

contain insignificant and probably ineffective concentrations of penicillin. Nevertheless, the surviving organisms multiplied so slowly that even in this

* Allowing as much as two hours for the period during which surviving organisms might continue to die faster than they multiplied, after the serum level of penicillin had fallen to less than the concentrations which are effectively treponemicidal in vitro.

20-hour "penicillin-free" period there was insufficient growth to affect the therapeutic activity of the preceding injection of penicillin. If, however, the interval between injections was still further prolonged, to e.g. three days, there was then ample time for multiplication, and the previously effective dose of 250 units/mg. was now wholly ineffective.[36] Indeed, on this twice

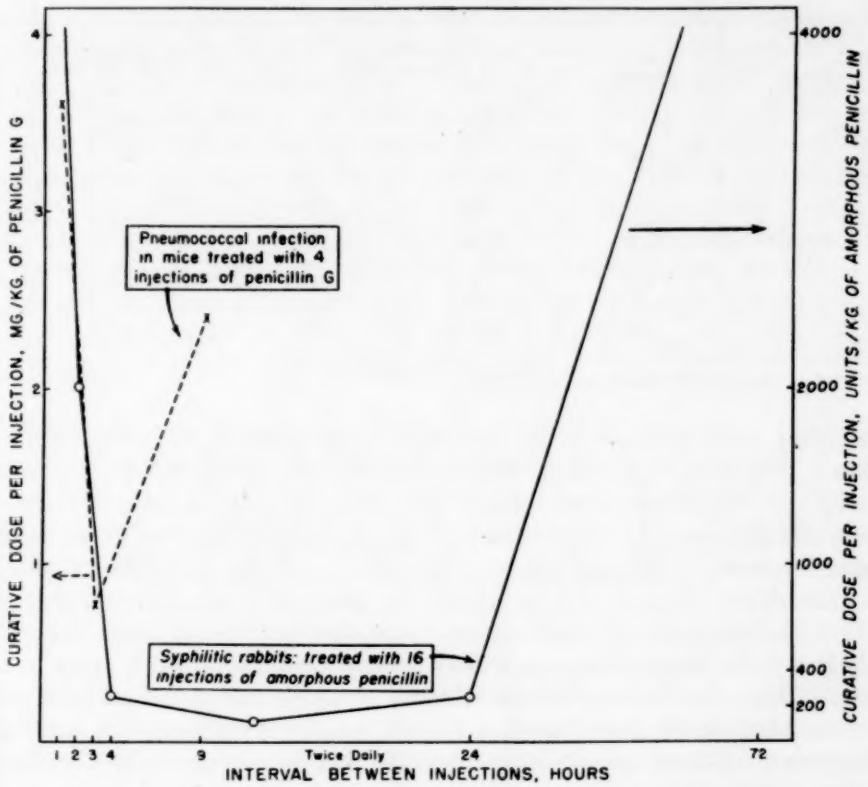

FIG. 8. The effect of the interval between injections on the curative dose of penicillin. In pneumococcal infections of white mice, penicillins G or X administered at 9-hour intervals were far less effective than the same dosages administered at 3-hour intervals, due to the rapid re-multiplication of survivors in the penicillin-free interval. In the case of syphilitic infection, however, and reflecting the slow multiplication of the organisms, the interval between injections could be prolonged to 24 hours without abolishing the therapeutic efficacy of the drug. With even longer time intervals between injections, however, the organisms multiplied sufficiently in the penicillin-free interval to counteract the effect of the preceding injection.

weekly schedule even dosages of 2000 units/kg. per injection failed to cure any of the animals.

A precisely similar situation was observed in the treatment of type I pneumococcal infections in white mice; but with this organism, since the average division time of the organism during the phase of active growth was 30 to 40 minutes, instead of 10 to 30 hours,[28] the maximum time for which

the penicillin blood and tissue levels could be permitted to remain below effective levels without affecting the outcome of treatment was correspondingly short. As shown in table 3, and figures 7 and 8, much larger doses were

TABLE III

The Effect of the Interval between Injections on the Curative Dose of Penicillins G and X in Pneumococcal Infections of White Mice (after Eagle[35])

No. of injections	Interval between injections, hours	Penicillin G CD_{50}, mg./kg.*		Penicillin X CD_{50}, mg./kg.*	
		per injection	total	per injection	total
Four	1	3.1	12.3	1.3	5.2
	3	0.8	3.2	0.32	1.3
	6	2.6	10.4	—	—
	9	2.4	9.6	0.85	3.4
	24	14.2	56.8	—	—

* Calculated after Reed and Muench.

necessary to effect cure if the injections were given at nine-hour intervals than if they were repeated at three-hour intervals. Thus, when penicillin G was given every three hours for a total of four injections, a dose of 1 mg./kg. cured 80 per cent (12/15) of the animals; but that same dose given at nine-hour intervals cured only 30 per cent (2/9). With penicillin X injected at three-hour intervals a dose of 0.5 mg./kg. cured all the animals tested (15/15); but given at nine-hour intervals, that dose cured only 33 per cent (5/15). As shown in figure 9, with both penicillins G and X, the curative dose (CD_{50}) on the nine-hourly schedule was two and a half to three times greater than on the three-hourly schedule. (The low therapeutic activity of injections repeated at one-hour intervals will be discussed in a following paper.)

In mice, penicillin G injected at 1 mg./kg. remains in the plasma at levels effectively pneumococcidal in vitro for approximately 1½ hours. When these doses were given at three-hour intervals, the "penicillin-free" interval was therefore on the order of 1½ hours; and in this period the organisms surviving the effects of the penicillin did not recover and multiply sufficiently to counteract the rapid bactericidal action of the drug (in vitro, 97 per cent killed in one and a half hours).[28] However, when the injections were given at nine hour intervals, the penicillin-free interval was then approximately 7½ hours. This permitted the surviving organisms to recover from the toxic effects of their brief exposure to penicillin, and to multiply sufficiently to counteract the bactericidal action of the drug. On this nine-hour schedule, one had to give three times as much penicillin to obtain the same results as on the three-hour schedule. It is a reasonable surmise that

the larger doses were effective, not by virtue of the higher blood levels they afforded, but because effective levels would then be provided for longer periods of time. More organisms would then be killed by each injection, fewer would be left to multiply during the penicillin-free interval, the duration of that interval would be reduced, and the balance would be restored in favor of the therapeutic agent.

In summary, although penicillin need not be maintained continuously at effective levels in order to effect cure, the maximum length of time for which those levels may be permitted to fall below concentrations which are bactericidal in vitro will vary from organism to organism. The "penicillin-free" interval between injections may contribute to therapy, but only so long as some of the surviving organisms continue to die, by whatever mechanism, at a rate exceeding that at which the others re-multiply. Once that therapeutically favorable balance is reversed, and once the rate of multiplication catches up with the rate at which the organisms can be destroyed, then the longer the time interval before the next injection of penicillin, the greater will be the degree to which the interim re-multiplication of organisms has counteracted the therapeutic effect of the preceding injection.

V. Schedules of Treatment with Penicillin Which Will Maintain the Serum Concentration in Excess of a Given Level [9, 31, 34]

In the light of the foregoing discussion, in the treatment of bacterial infections with penicillin it may be desirable to know the average time period for which a given dose would provide serum concentrations in excess of a given value; or conversely, how often a given dose of penicillin must be repeated in order to maintain that serum level. Such data can be used only as a rough guide to treatment in view of the large and varying differential between the serum concentration of penicillin and that at the focus of infection (cf. page 265); but by and large, the provision of a 2- to 10-fold excess in the serum will assure the presence of the maximally effective level in most tissues.

Figure 3 (after [9]) shows the average blood levels after the intramuscular administration of aqueous penicillin G at dosages of 10, 3, 1.5, and 0.6 mg./kg., corresponding to total dosages of 1,200,000, 360,000, 180,000 and 72,000 units in the average adult. In table 4 (from [9]) these data have been used to calculate the dosage of penicillin necessary to sustain a serum concentration in excess of a given level for a period of one, two, or four hours. Finally, table 5, also after Tucker and Eagle,[9] indicates the frequency with which a given injection should be repeated in order to maintain a given plasma level. Thus, as shown in vertical column 8 of that table, in order to assure the constant presence of at least 1 microgram (1.6 units) per c.c., one may inject 720 mg. (1,200,000 units) every three to four hours, 360,000 units every 2 hours, or 180,000 units every hour.

At the present writing, similar tables and figures cannot be constructed for penicillin in oil and beeswax, and for two distinct reasons. The first is

the fact that with this preparation, there is greater variation among individual patients in the rate of absorption than is the case with the aqueous solutions. The second and more disturbing fact is that different commercial preparations of penicillin in oil and beeswax vary markedly in the length of time for which they provide a given serum level of penicillin.[9]

VI. Recapitulation and Discussion

The blood penicillin level is of significance insofar as it provides a rough measure of the concentration at the foci of infection in the tissues. The curve

Table IV

Amount of Penicillin G in Aqueous Solution Which Must Be Injected at Given Intervals in Order to Maintain a Desired Plasma Level (Tucker and Eagle[9])

Interval between injections (hours)	To maintain a plasma concentration of penicillin G in excess of							Micrograms per c.c. Units per c.c.
	0.1 0.16	0.2 0.32	0.5 0.8	1.0 1.6	2.0 3.2	5.0 8.0	10.0 16.0	
	the following dosages must be given at the intervals indicated in the left hand column (upper left hand figure in each block is dosage in mg./kg.; lower right hand figure is the total dose in units in average adult)							
1	0.16 20,000	0.35 40,000	0.74 85,000	1.3 150,000	2.1 250,000	4.2 500,000	9.1 1,000,000	
2	0.45 50,000	0.95 100,000	1.9 220,000	2.7 330,000	4.7 550,000	11.5 1,300,000	— —	
3	1.2 140,000	1.9 220,000	2.9 340,000	5.7 675,000	11.5 1,300,000	— —	— —	
4	2.0 235,000	2.8 330,000	7.4 855,000	11.4 1,300,000	— —	— —	— —	
6	5.2 600,000	8.8 1,000,000	— —	— —	— —	— —	— —	
8	12.0 1,400,000	— —	— —	— —	— —	— —	— —	

of those tissue levels after an injection of penicillin is probably of major importance in relation to its therapeutic efficacy, and may be expressed in terms of three time periods: the length of time for which penicillin is present at maximally effective concentrations which kill the organisms at the fastest possible rate; the time for which penicillin is present at somewhat lower concentrations, which are more slowly bactericidal; and finally, the time period, after the penicillin has fallen to concentrations lower than those which kill the bacteria in vitro, but during which the organisms continue to die in vivo at a rate faster than they multiply. Whether this continuing death in the apparently penicillin-free interval is due to the fact that penicillin persists in the tissues longer than it does in the blood; whether organisms are killed by lower concentrations of penicillin in vivo than they are in vitro, due to the participation of the body's defense mechanisms; or whether organisms exposed to penicillin recover from its toxic effects only slowly, and during that

temporary period of retarded multiplication are disposed of by the cellular and humoral defense mechanisms of the host, are as yet open questions.[26, 32] In any event, this third period of gradually disappearing penicillin activity provides a margin of safety, in that the blood and tissue penicillin levels may be permitted to fall below those which are significantly bactericidal in vitro without affecting the outcome of treatment.

TABLE V

Frequency at Which a Given Dose of Penicillin G in Aqueous Solution Must Be Injected in Order to Maintain a Desired Plasma Level (Tucker and Eagle[9])

				To maintain a plasma concentration of penicillin G in excess of						
				Micrograms per c.c. / Oxford Units per c.c.	0.1 / 0.16	0.2 / 0.32	0.5 / 0.8	1.0 / 1.6	2.0 / 3.2	5.0 / 8.0	10.0 / 16.0
Dosage per kg.		Total dose in average adult		the injections indicated in the left hand column should be repeated at the intervals (hours) indicated in the body of the table						
mg.	units	mg.	units							
10	16,700	720	1,200,000	8.0	6.0	4.5	3.5	3.0	2.0	1.2
3	5,000	216	360,000	5.0	4.0	3.0	2.0	1.6	0.6	—
1.5	2,500	108	180,000	3.0	2.5	1.7	1.2	0.8	—	—
0.6	1,000	43	72,000	2.0	1.5	0.8	—	—	—	—
0.3	500	22	36,000	1.6	0.9	—	—	—	—	—
0.15	250	11	18,000	0.9	—	—	—	—	—	—

Eventually, however, the surviving organisms do recover from the toxic effects of penicillin to the degree that they multiply faster than they can be killed, and thus counteract the effect of the preceding treatment. If this is permitted to continue for only a brief period before the injection is repeated, the effect of treatment is counteracted only in part. More organisms are killed by each injection than reappear between injections; and provided that treatment is continued for a sufficiently long period of time, the patient may ultimately recover. If, however, too long an interval is permitted between injections, the effect of treatment may be wholly counteracted by the intervening re-multiplication of the surviving organisms. As has been indicated in the present paper, the danger is greater with organisms which recover rapidly from the toxic effects of penicillin, or which multiply at a fast rate, than it is in the case of organisms which multiply only slowly (*T. pallidum*).

Large injections of penicillin are more effective than small injections, not because they provide higher absolute levels of penicillin, but because they provide the effective concentrations for longer periods of time. More organisms are then killed by each injection, and fewer survive to re-multiply in the interval between injections. Further, that interval may then be prolonged, because with fewer surviving organisms, less harm is done by a penicillin-free interval of multiplication.

It is obviously not necessary to maintain the blood and tissue concentrations of penicillin continuously at effective levels in order to attain cure. The most rapidly effective method of treatment would nevertheless be to repeat injections at such frequency as to maintain the tissue levels continuously in excess of that concentration which kills organisms at the maximum possible rate. (This could be achieved also by continuous intravenous, intramuscular or subcutaneous infusion at a rate designed to maintain at the focus of infection that level maximally effective for the specific organism.) However, this generalization requires qualification in at least two respects.

The first is the possibility suggested by Bigger [33] that, since bacteria are killed by penicillin only while they are multiplying, a continuously maintained level of penicillin may fail to kill those organisms which happen to be present in a physiologically inactive resting phase. Those hypothetical resting organisms ("persisters") would become vulnerable to the action of penicillin only if they were permitted to resume multiplication. Bigger suggests that intermittent treatment might therefore be more effective than continuous treatment, since the persisters would resume multiplication in the penicillin-free interval and thereby become vulnerable to the succeeding injection of the drug. There has as yet, however, been no convincing demonstration in either animals or men that intermittent treatment, i.e., periods of effective concentrations separated by penicillin-free intervals, are in fact more effective than continuously maintained levels.

The second qualification is due to the fact that certain organisms are killed more rapidly at low concentrations of penicillin than they are at high concentrations.[8] All of four strains of group B β-hemolytic streptococci, two of four strains of group C organisms, five of seven strains of *Streptococcus fecalis*, three of four strains of other α-hemolytic streptococci, and four of nine strains of staphylococci were found to give this paradoxical zone reaction. With such organisms, a continuously sustained level provided by a continuous intravenous or subcutaneous infusion might therefore be more effective therapeutically than the rapidly changing blood levels afforded by intramuscular injections of penicillin in large dosage, since with the latter method the optimally effective concentration would be present for only a short period of time.

If the thesis elaborated in the present paper is correct, then the therapeutic activity of a given dosage of penicillin rests in large part, if not primarily, on the total length of time for which it remains at bactericidal levels, with particular emphasis on the time for which it is present at the maximally effective concentration, plus the time required for the organisms to recover from the drug and effectively resume multiplication. The enormous differences observed in the curative dose of penicillin when either the number of injections or the interval between them is varied,[29] should rest primarily on the total time period of effective penicillin action.[5] Conversely, different schedules of treatment which have the same biological effects (e.g. 50 per cent cure in a

given infection) should provide effective levels for the same total period of time,* whether the curative dose on those equi-effective schedules is 200,000 or 200 units/kg. An experimental demonstration of this relationship will be discussed in a following paper.[35]

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* Properly weighted for the varying rates of bactericidal action at varying concentrations of penicillin, and corrected for re-multiplication between injections.

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PSYCHIATRIC ASPECTS OF VAGOTOMY: A PRELIMINARY REPORT *

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INTRODUCTION

THERE has been a great deal of interest in vagotomy, as a therapeutic technic for peptic ulcer, ever since its introduction by Dragstedt [1] four years ago. Several excellent papers have appeared subsequently on the indications, physiologic effects, and clinical results of this treatment.[2, 3, 4, 5, 6, 7] However, no report has appeared in the literature, to date, on any systematic psychiatric studies of patients subjected to vagotomy. Due to the interest and helpful coöperation of Dr. Lester R. Dragstedt and Dr. Walter L. Palmer a study of a number of such patients was made possible. This study has now been in progress for approximately eight months, a rather brief period for a project of this type. However, certain preliminary conclusions can be formulated which are considered of sufficient interest to warrant presentation at this time.

CLASSIFICATION OF CASES

This preliminary report is based on a study of 16 patients. All patients but one were referred routinely; one individual was referred because of symptomatic psychiatric difficulties. Detailed anamneses were obtained from all patients and most were seen in more than a single interview; five of the patients were studied in great detail, each having been seen in 10 or more interviews. All but one of the patients were men. In age, they ranged from 23 to 65 years. The duration of the ulcer symptoms ranged between three and 45 years. There was roentgen evidence of ulcer, before vagotomy, in all of the patients. Only one had a gastric ulcer; in the remaining 15 the ulcer was in the duodenum. Eleven patients were seen only after vagotomy, and five both before and after. The operation performed in each case was a subdiaphragmatic vagotomy; a gastroenterostomy was also done in all but one of the patients. Except for one patient who was operated upon in June 1945 and who was subsequently referred because of psychiatric illness, all the others were operated upon between June 1946 and February 1947; the period of follow-up on these patients thus ranges from two to 10 months.

RESULTS

It seemed best to consider the results following vagotomy from two different points of view; the data were therefore analyzed in an attempt to answer the following two questions:

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1. What happens to the ulcer?
2. What happens to the patient?

At present it is possible to answer the first question with some degree of definiteness. If the section of the vagi is complete, the ulcer heals and apparently does not recur.[3, 4] This has been true for approximately 200 patients operated upon by Dragstedt [8] during the past four years.* In the present series, the ulcer has healed and has not recurred, up to the present time, in 15 out of the 16 cases. The patient whose ulcer has not healed yet was operated upon in January 1947; two months later, the ulcer crater, though of decreased size, was still demonstrable roentgenologically in the pylorus. The possibility of malignancy could not be ruled out, and this patient is under close observation at the present time.

The answer to the second question, namely, "What happens to the patient?" is a tentative one and is based largely on observations in this series of cases. The results have been classified under three clinical headings; this was based essentially on (a) whether or not the patient developed other symptoms following vagotomy, and if so, the nature, severity, and incapacitation suffered therefrom, and (b) the nature of the patient's social adjustment following vagotomy.

TABLE I

Results

	Number of Patients	Per Cent
1. Improved	9	57
A. Good results	6	38
B. Fair results	3	19
2. "Status quo ante"	6	37
3. Poor results	1	6
Total	16	100

For criteria employed in evaluating results see text and footnote, page 281.

1. *Improved.* Nine of the 16 patients fall into this group, which has been further subdivided as follows:

A. *Good results.* Six patients have resumed their former occupations and are free from gastrointestinal as well as other symptoms.

* The first and only patient with what was thought to be a complete vagotomy who developed a recurrence—or more precisely a new ulcer—came to our attention very recently. This man (W. C. B.), age 63, was the first patient to undergo supradiaphragmatic vagotomy in this hospital (January 1943). He was without gastrointestinal symptoms until about six months ago; he then noted recurrence of ulcer pain relieved by milk and antacids. Roentgen examination revealed a huge ulcer crater on the lesser curvature of the stomach. The results of the tests used to determine the completeness of the vagus section (insulin test and night secretion studies) indicated that the vagotomy was a complete one. On operation (April 11, 1947) a huge ulcer was found on the lesser curvature of the stomach and subtotal gastric resection was performed. At this operation, a nerve fiber to the stomach, thought to be part of the vagus, was found and excised; histological study of this specimen showed intact nerve fibers; it is thus questionable whether or not this patient has had a complete vagotomy. Histological examination of the ulcer showed no evidence of malignancy. It is of interest to note that prior to vagotomy the patient's ulcer was in the duodenum.

B. *Fair results.* Three of the 16 patients fall into this group in which were included patients who are not entirely free of symptoms but in whom vagotomy was, on the whole, of benefit. (For the purposes of this classification the common, early post-operative symptoms of fullness after eating, "bloating", and slight diarrhea have been disregarded; these are, apparently, primarily physiologically determined and usually disappear in a few months.) Two patients in this group were annoyed by an increased frequency and intensity of feelings of hunger; one of them found it necessary to drink warm milk, every night, before he could fall asleep; and occasionally he drank some milk between meals. He had no ulcer symptoms.

2. *"Status quo ante."* Patients in this group, though completely healed of their ulcer (except for one, referred to earlier, whose ulcer has not yet disappeared completely) continued to have some type of difficulty; some complained of symptoms closely resembling those which they experienced prior to vagotomy; others developed new symptoms of approximately equal severity. From the point of view of the patient as a whole, except for the healing of the ulcer, the status of these individuals was essentially unchanged by vagotomy.* Six patients fall into this group. Five individuals continued to complain of various abdominal symptoms; and three of these were relieved by milk and/or dietary restrictions (sometimes self-imposed). One patient became a heavy drinker.

3. *Poor results.* Only one patient in this series falls into this group; he is the one who was referred because of psychiatric illness. This man, though his ulcer is healed, is completely incapacitated socially. He is a 49 year old engineer who had had a duodenal ulcer for 17 years before he was operated upon. There was a history of a period of addiction to opiates, four years prior to vagotomy. This patient developed hysterical conversion symptoms four months after operation; he also resumed taking opiates whenever he could obtain any; and his total behavior was one of intense infantile dependence; he was a psychological invalid. Seventeen months following vagotomy he still felt unable to work, and when last heard of he was getting "treatments" from a chiropractor.

In evaluating the results it must be borne in mind that the period of follow-up has been rather short; the error, therefore, is likely to be in favor of the first group.

Psychologic Factors in Peptic Ulcer

In order to make this analysis more meaningful as well as to more clearly evaluate vagotomy from a psychiatric point of view, we must consider briefly our concepts concerning the rôle of psychologic factors in the pathogenesis of peptic ulcer. Unfortunately space does not permit a detailed con-

* This statement does not give sufficient consideration to the healing of the ulcer per se, and thus the prevention of potential complications (e.g., hemorrhage, perforation) from this source alone. This prophylactic value of vagotomy does not find expression in the above classification of results.

sideration of this subject.[9, 10, 11, 12, 13, 14, 15] The psycho-physiologic chain of events which may lead to the formation of a peptic ulcer is shown in a simplified and schematic form in table 2. This is based largely on Alexander's work.[9, 10] As shown in this table, it is the conflict between powerful dependent needs and strivings for independence, and the regressive solution of this conflict in the face of frustration of the "receiving" tendencies, which is of crucial importance for the development of an ulcer.

TABLE II

Probable Chain of Events in the Pathogenesis of Peptic Ulcer

I. Conflict (Unconscious)

Dependence ("Being taken care of like an infant" "Receiving") ⟷ Independence ("Taking care of others like an adult" "Giving")

II. Frustration of dependent needs
1. Internal (superego)
Dependent tendencies are ego-alien (unacceptable)
2. External (reality)
Patient would accept dependent rôle but he is, in reality, not a child any more; society demands adult rôle.

III. Regression
1. Psychologically: return to the level of the suckling infant; love and security are equated specifically with feeding, and more generally with "receiving."
2. Physiologically: stomach is in an almost continuous state of preparation for receiving food; it "behaves" like the stomach of the suckling infant. This state of affairs is brought about (mediated) by a hypertonus of the secretory and motor fibers of the vagi.

IV. End Result
Morphological change in the upper gastrointestinal tract: peptic ulcer.

Let us now compare the time-tested medical therapies for peptic ulcer[16] with vagotomy, in the light of what is known about the rôle and significance of psychologic factors in this disease. From the physiologic point of view, there are certain basic similarities between these two anti-ulcer therapies. Both attempt to influence the increased and continuous secretion of acid gastric juice. Frequent feedings, milk, cream, and antacids accomplish this by buffering (neutralization) of the acid. Vagotomy achieves a similar end result by a fundamentally different method: the neural pathway which mediates the increased gastric secretion is sectioned. Gastric acidity—and particularly the night secretion—is thus reduced; the altered gastric motility also may be of some significance in the healing of the ulcers.

Consideration of the physiologic effects of these two fundamental approaches to the treatment of peptic ulcer, however, gives no inkling about the psychologic aspects of the problem. It must always be borne in mind that whatever therapeutic technic may be used—be it bed rest, diet, chemotherapy, or surgery—it has certain psychological *meaning* to the patient.[17] This aspect of the treatment is of particular importance in peptic ulcer. As indicated earlier, these patients have a great need to "receive"; and incorporation via the gastrointestinal tract is particularly meaningful to them. As a

matter of fact, experienced physicians frequently understand this intuitively. For example, it is well known that many ulcer patients experience striking relief of their symptoms as soon as they are hospitalized, even though essentially the same medical regime is continued as was used at home. A recent article in Lancet by A. M. Gill [18] will further amplify this point about the *meaning* of therapy. He writes: "A consecutive series of 20 patients, each with a chronic gastric ulcer, were given a daily hypodermic injection of 1 c.c. of distilled water. They were ambulant, their diet was unrestricted and even disregarded, they were given no medicines, and those who enjoyed smoking were encouraged to continue. With one exception all lost their pains as quickly—i.e., within a few days—as a control series treated along orthodox lines. Healing of the ulcers was observed gastroscopically and took place in the usual time—i.e., in four to eight weeks from the start of treatment." What does all this mean? It means simply that being in a hospital or getting "shots" *means* something to the patient, something which is very important. Just as in everyday language we can differentiate between the denotation and the connotation of a word—so in therapy, medical or surgical, we should think of the "connotation" of our specific therapeutic technic. In other words, we should consider the *unconscious meaning of the procedure to the patient.*

This brings us to the important difference between the medical management of ulcer and vagotomy. The frequent ingestion of milk and cream does more than just buffer (neutralize) free acid; it has the meaning of actually receiving food, and unconsciously this stands for affection and security. The close resemblance of the Sippy regime to the feeding schedule of the young infant has been pointed out many times before, but its significance cannot be overemphasized. This, however, should not be confused with what is called the "secondary gain" in neurosis; we are referring to the symbolic and unconscious meaning of the therapy—the satisfaction of an emotional (instinctual) need.

In contrast to the above, vagotomy brings about the physiological changes necessary for the healing of the ulcer without providing any gratification for the patient's needs to "receive." It therefore seems especially significant that the ulcers heal, and do not recur, in spite of the fact that these important emotional needs remain ungratified and the basic conflict remains unchanged. From the purely physiologic point of view, this is only further evidence for the fundamental soundness of vagotomy in abolishing the ulcer. From the psychiatric as well as from the general clinical point of view, however, an important disadvantage of vagotomy may lie in this very absence of providing gratification for the patient's dependent (oral) needs. This is illustrated by several patients: three in the present series, and one reported by Moore and his associates in a recent paper. The three patients in this series obtained relief from abdominal pain and discomfort by drinking milk, even though their ulcers were healed. And Moore [6] writes: "The fifth (patient), while

clear of disease roentgenologically, is now two years postoperatively, again taking antacids and milk for 'ulcer pain.'" The meaning of this self-treatment should be clear in the light of the foregoing discussion. Freud has admonished us always to pay attention to what the patient tells us; and if these patients tell us that they need milk—we should listen, even if they do not have an ulcer any longer! Their continued need for, and insistence on, milk and antacids is an important clue to our understanding of the problem of peptic ulcer.

Our understanding of the pathogenesis of peptic ulcer has been helped considerably by the study of vagotomized patients. The evidence very strongly suggests that man does not develop peptic ulcer * if the vagi are completely sectioned. Among all of the patients operated upon by Dragstedt there has not been a single instance of recurrence, if the vagus section was complete; † a truly amazing record.

That emotional stimuli are mediated from the central nervous system to the stomach via the vagi is not a new concept. In 1936, Alexander [10] stated: "Obviously the psychic stimulus is led to the stomach through parasympathetic pathways." The evidence for this is now conclusive:

1. The ulcers heal and do not recur following vagotomy. This occurs in spite of the persistence of the emotional conflicts etiologically related to the production of ulcer in the intact human being.
2. There is a reduction in the volume and acidity of the continuous night secretion to normal, following vagotomy; the response to sham feeding is abolished.
3. In one of our cases we demonstrated a marked increase in the acid gastric secretion when the patient experienced anger; this effect was abolished by vagotomy.[13]

Comment

In conclusion, let us consider the therapy of peptic ulcer from the psychiatric point of view—or to put it differently—from the point of view of the patient as a whole. In considering this problem, Alexander, in "The Medical Value of Psychoanalysis," [10] stated: "Undoubtedly in all psychogenic cases only psychoanalysis can be considered as an etiological therapy, because in the long chain of events that finally lead to ulcer formation, the chronic psychic stimulus (the repressed wish to be loved, to be fed) is the first link." And Dragstedt,[3] in a recent paper, wrote as follows: "The central nervous

* The term "peptic ulcer" is used to denote the "usual clinical case" of peptic ulcer; cases of either Cushing's ulcer [19, 20] or Curling's ulcer [21] are not to be included under this heading. Vagotomized patients, of course, could not be expected to develop a Cushing's ulcer. The development of Curling's ulcers on the other hand cannot be expected to be preventable by vagotomy; however, we know of no report in the literature, to date, of such a case, in a vagotomized person. Ulcers have been produced in vagotomized animals (dogs, cats, and rabbits) with histamine.[22]

† This statement may have to be modified somewhat in the light of recent experience; see footnote, page 280.

system disturbance causes ulcers by producing a hypertonus in the secretory and motor fibers in the vagus nerves. While the severing of these nerves prevents nervous tensions of various kinds from affecting the stomach, it cannot be considered the final answer to the ulcer problem. Perhaps this may lie in adjusting the individual to his work and environment so that these tensions do not arise."

Most psychiatrists now believe that emotional factors are of paramount etiological importance in a very large percentage of cases of peptic ulcer. That not all patients can be, or even need be, subjected to psychoanalysis is obvious [23]; perhaps the briefer methods of psychoanalytic therapy will prove to be of practical help to an ever increasing number of patients.[24, 25] Still, it must be remembered that most patients with peptic ulcer are now and, probably for a long time to come, will be treated by the general practitioner, the internist, the gastroenterologist, and the surgeon. What recommendations can the psychiatrist offer regarding the treatment of these patients in general, and vagotomy in particular? We want to preface our suggestions by restating the belief that the optimum treatment for patients with peptic ulcer is psychoanalytic therapy. This conclusion follows inevitably from our concept of the disease; in most cases the lesion in the upper gastrointestinal tract is but one manifestation of an emotional illness involving the total personality. The question, however, which must be answered at this time is, "How to manage patients who, for whatever reason, will not be treated psychotherapeutically?" Further comments will apply to this group of cases only.

Since many patients with uncomplicated peptic ulcer respond so readily to even simple medical regimens, it would seem best to treat such patients conservatively. Vagotomy, however, has, and will continue to have, an important place in the treatment of peptic ulcer. It is certainly the most physiological of all the surgical procedures used in the treatment of this disease. Section of the vagi interrupts the "final common pathway" in the chain of events leading to the formation of ulcer. There seems to be no more direct, nor more effective technic, at the present time, for bringing about the healing and the prevention of peptic ulcer. Almost any patient, therefore, in whom the ulcer cannot be made to heal, or cannot be prevented from recurring, with the usual medical measures of diet, milk and cream, and antacids, may benefit from vagotomy (except when the procedure is contraindicated for specific medical or surgical reasons).[6, 26] Even symptomatic (i.e., other than ulcer) psychiatric illness is, per se, not a contraindication to vagotomy. It should be emphasized, however, that the abrupt discontinuation of medical measures may be psychologically harmful to these as well as to many of the other patients. The value of vagotomy is now well established and it is therefore no longer necessary to instruct patients to discontinue all pre-operative medical measures—which, true enough, physiologically they no longer need, but which may continue to help them greatly psycho-

logically. This is particularly true of the taking of milk which becomes a habit with many ulcer patients. We would advocate that patients be permitted to continue with such "medical" measures for some time following vagotomy, and if need be indefinitely. ("Weaning" should not be abrupt!) A combination of the unmatched physiologic advantages of vagotomy with the psychologically meaningful aspects of the usual medical anti-ulcer measures may yet prove to be the best (non-psychoanalytic) method of therapy for these patients.

Summary

The clinical results in a group of patients studied carefully from the psychiatric point of view and operated upon for peptic ulcer by resection of the vagi are presented.

In all cases but one the ulcers have healed and there have been no recurrences, to date, in the present series. Clinical results, however, cannot be based on the fate of the lesion in the gastrointestinal tract alone. In answer to the question, "What happens to the patient, as a whole, following vagotomy?", the following answer was found. A little over half (57 per cent) of the patients in this series have been definitely helped by vagotomy. Six patients (37 per cent) were found to be "status quo ante," from the psychiatric and clinical points of view; the healing of the ulcer, however, confers protection on these patients against future complications from this source (e.g., hemorrhage, perforation). This prophylactic value of vagotomy does not find expression in our present classification of results. One patient became definitely worse following vagotomy and remained incapacitated (psychologically) during the period of observation.

The rôle of psychologic factors in the pathogenesis of peptic ulcer is discussed. Patients suffering from this illness have a strong need to "receive." These receptive-acquisitive tendencies obtain some (partial) gratification from the usual medical measures used in the treatment of peptic ulcer; vagotomy brings about healing of the ulcer without providing for these important emotional needs. This explains why some patients insist on continuing with some part of their medical regimen (e.g., taking milk) after vagotomy, when the physiologic needs for such treatment are no longer present.

Psychoanalysis is, in our opinion, the only etiologic treatment in most cases of peptic ulcer. This type of treatment, however, is of limited applicability and is not available for the large majority of patients at the present time.

For those patients who do not respond adequately to the usual medical ulcer regimens and who, for whatever reason, will not be treated psychoanalytically, vagotomy is probably the treatment of choice. The absence of symbolic oral gratification due to cessation of dietary and other medical measures following vagotomy is thought to be potentially harmful. It is

suggested that the clinical results may be improved somewhat if the patients are permitted (possibly even encouraged) to continue with certain psychologically meaningful aspects of their preoperative medical regimens after vagotomy.

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THE RÔLE OF ANXIETY IN SOMATIC DISEASE*

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I. STRUCTURE AND FUNCTION OF THE ANXIETY MECHANISM

ANXIETY reactions to organic disease follow the same principles as those which govern the generation of anxiety in general. In a given situation which constitutes a threat to the interests of an organism there occurs a somatic mobilization which is reactive to the danger and preparatory for coping with it. The most easily perceived effects of this are referable to the heart and the respiratory organs. Motor innervations also take part in this reaction. In the human being awareness of these events constitutes the actual unpleasant sensation of anxiety.

The mobilization of anxiety may be vestigial or quite complete. Thus there may be a transient epigastric sensation, a few extrasystoles, a sharp inspiration, and a slight tensing of the skeletal musculature. Or, the heart may assume a steadily increased force and rate, accompanied by increased ventilation, and vigilant exploratory activity. If the danger then materializes the organism is aware of and ready for the alternative—fight or flight. We see thus that anxiety is not merely a symptom. It has a very definite function in the interest of survival. It is, so to speak, a readying mechanism which clears the deck for action.

Beginning very early, human beings internalize the objects of the environment and the relationships which exist among them. Language function and the capacity for imagery make this possible. In consequence the anxiety mechanism operates in response to various types of psychic representations of danger.

II. DEVELOPMENTAL HISTORY OF THE ANXIETY REACTION

The dangers to which the human being responds with anxiety are derivatives of those which appear and have paramount importance at successive stages in the development of the personality.

At the very earliest stage, survival is the outstanding problem. The inability of the infant to do anything about this without assistance is obvious. The first anxiety situation is the powerlessness of the infant to cope with internal tensions produced by the needs arising from hunger, cold, pain, and postural insecurity. The first consequence of the mobilization of the anxiety mechanism is the helpless cry which, together with the unorganized movements of the infant, serves only to discharge tension.

At the next stage the child has made a more or less clear identification of

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the mother as the agent of the relief of tension. The leading danger situation then becomes the absence of the mother. The tensions belonging to hunger, or discomfort, need no longer be immediately present to produce the anxiety signal and the infant's cry. Separation from the mother is now enough. The infant's cry is no longer helpless but help-bringing. For the first time anxiety is seen to be functional rather than simply reactive to tension. Now the infant is able to govern its environment.

In consequence of the further maturation of the nervous system, the powers of perception improve and become integrated with the powers of manipulation and locomotion. More or less active mastery of the environment now becomes possible. The organism becomes more dependent on its own sensory-motor capacities to govern the environment in its interest. The complete elaboration of these capacities goes on until adulthood. With their first appearance, however, comes the anxiety which is connected with any threat to physical integrity. Any threat to the powers of overt activity now is tantamount to a threat of return to the helplessness and dependence which had previously characterized the state of the infant. The adaptive response to anxiety is now characterized by an attempt at physical mastery.

The maturation of the physical powers of mastery brings the individual to the final stage of integration, that which finds him in a social relationship to other people. The social structure, rather than the physical environment now establishes the criteria of survival. By means of the technics of the particular culture, the person now aims at success, security, status, and power. The anxiety stimulus now resides primarily in negative factors that militate against such attainments.

To these are added the burden of social disapproval of certain strivings. Such sanctions are derived from traditional prohibitions and regulations which were at first imposed through parental authority. Ultimately they are reinforced and maintained by self-controlling and self-regulating mechanisms which the person experiences as self-esteem and self-depreciation. Together these factors constitute checks upon the unlimited expression of egoistic impulses. If these checks reach a certain intensity they operate as stimuli to the anxiety mechanism. Thus the threat of business failure produces anxiety; the threat of loss of reputation, whether this be a matter of ethics or pertains to one's professional capacity, produces anxiety; threats to self-esteem produce anxiety. Dangers of this order are the final social derivatives of the earlier danger of maternal desertion, and of the later encountered danger of injury to physical integrity when parental authority and restrictions intervene.

We may finally re-state the various levels from which the stimulus to anxiety arises: The threat of complete helplessness derives from earliest infancy. The threat of separation from those to whom we have a necessary relationship stems from the dependence of the young child on the mother. The threat of physical injury originates in the value placed by the child on

his self-assertive powers. Lastly, the threat of social disapproval or of the loss of self-esteem derives from the final internalization by the child of taboos and restrictions on his egoistic strivings insofar as these violate the prerogatives of the other members of the family group.

In any given person, depending on various factors which make him finally the personality he happens to be, one or the other of these sources of anxiety will tend to predominate. All persons are capable of deriving the stimulus to anxiety from any of these sources depending on the circumstances.

III. Illness and Trauma as Anxiety Stimuli

Illness and trauma constitute frontal attacks on the basic security of the individual. Somatic self-sufficiency is impaired or destroyed; the person is forced back on the path of his emotional development to dependency on other persons. Uncertainty about the reliability of these persons may reach into the deepest levels of feeling and revive primitive anxiety tension. Because our culture emphasizes independence and self-sufficiency as prime virtues, the incapacity and helplessness produced by illness may secondarily affect the person as if he were a victim of retribution for the secret guilts which in one degree or another most people harbor. For similar reasons illness may also be looked upon as a desertion by fate, by luck, or by the particular divinity in whom the person believes. Finally, certain illness may be stigmatized as specifically revealing a person's weakness or unworthiness. Whatever the individual case may be, a quota of anxiety is added to the burden imposed by the disease or injury itself and the clinical picture is directly influenced by the anxiety and by the particular reactions of the person to it.

Before going further, it is necessary to emphasize the fact that anxiety is not merely an unfortunate complication of somatic illness. Let us assume an ideal condition of somatic illness. The patient feels somehow indisposed, recognizes there is something wrong, decides that he had better lay off for a while before he gets worse, and goes to bed. The next morning he is still sick. There is work to be done but that will have to wait. There may be really something wrong with him. He permits his wife to serve him his breakfast in bed, to tend to him, and finally to call the doctor. The diagnosis is pneumonia. The patient has confidence in his physician, follows his orders, accepts his treatment and shortly he is convalescent and back on the job.

If we consider this situation from the standpoint of our discussion we see that here the anxiety reaction to the threat of illness has been minimal but nevertheless sufficient to serve the purpose of inducing a regression to a level of organic function which established optimum conditions for recovery. The regression to passivity seen here is a flight reaction which is necessary to the survival of the sick organism. It is a sort of strategic retreat. This is a normal psycho-biological characteristic of all illness and demonstrates the adaptive rôle of anxiety.

IV. Clinical Demonstrations of Anxiety Reaction to Illness

Returning now to the consideration of anxiety as a pathological component of somatic illness we are presented with the possibility of deviations in several directions: (A) Anxiety may eventuate in a more than necessary functional regression to passivity and dependence. (B) It may be repressed and produce secondary complicating symptoms. (C) It may lead to reactions *against* itself.

(*A*) *Excessive Regressive Reactions to Illness Anxiety.* In the first group the cases will run the gamut from anxious agitation about a pimple through delayed convalescence, to chronic invalidism and complete surrender.

All of us are familiar with fearful patients of the first type. These problems belong among the neuroses.

The problems of convalescence are somewhat different. As has been shown, every illness induces a certain degree of functional regression. This resumption of childlike helplessness is accompanied by a corresponding contraction of the person's interests. His world narrows down to himself and his immediate needs. He resumes the egocentricity of childhood and becomes demanding, intolerant and domineering. In part this is a means of controlling his environment despite his helplessness. In part it is a protest against the helplessness which makes him dependent. For the patient is at one and the same time grateful to those who care for him and resentful of the incapacity and insecurity which make this necessary.

During normal convalescence there is rapid reintegration of the impulse to active mastery. In cases of delayed convalescence psychic reintegration tends to lag behind somatic restoration of function. We have the clearest example of this in fracture cases in which the injured member may be mechanically useful long before the patient uses it. The developmental precursor of this situation is illustrated in the child's learning to walk. Functional capacity may be present here for some time before it is actually exploited. Some children begin to walk earlier than others not because of differences in neuro-muscular development but because of a different capacity for tolerating the anxiety which is induced by the new problem of integration. Similarly, patients will tend to cling more or less to the simpler integration which illness induces. They seem to have lost the feel of their former capacity for mastery of a more complex world than that of the sick room. The final result is determined by two variables—the severity of the illness or trauma and the individual's tolerance for anxiety. Convalescence is thus seen to be a process which recapitulates the original problems of development and with these the original signals for anxiety.

The chronic invalidism which may follow an illness is an outgrowth of the normal problems of convalescence when these are complicated by a number of other factors. Given equal severity of illness or injury, the patient's tolerance for the anxiety-inducing problems of convalescence will

vary with his constitution, with his previous success or failure in mastering anxiety-inducing threats, and finally with the secondary gains of illness. Clinical examples will demonstrate this.

Example 1. A 19 year old male was admitted to the clinic with complaints of weakness, fatigability, vague chest pains. Two years previously he had been hospitalized for pleurisy with effusion and subsequently resided at a preventorium for six months as a tuberculosis suspect. The diagnosis was never confirmed and he was discharged in apparently good health. Since then he had remained indolently at home, felt unable to engage in any activity, was apathetic and interested only in his physical condition.

Examination was unrevealing of any somatic disease.

The social service investigation revealed that he came from a run-down family, the father an alcoholic, the mother a dull woman who submitted to the father's brutalities, and took care of a large brood of children. The family was on relief. The patient had been slow to learn to talk and walk and had left school at age 14 after completing only six grades. He had been a sickly child, had had chronic otitis media and had never been able to hold his own among seven siblings of whom he was the fourth. After leaving school he had worked sporadically as a news vendor and errand boy until he became ill with pleurisy. At the preventorium he had had a record of exemplary behavior, seemed contented and was not eager to leave.

Here we have an individual who seems never to have had enough of the wherewithal to tackle the problems of living. His chronic invalid reaction seems largely to represent a consequence of this fact.

Example 2. A 48 year old male was admitted to the hospital with a fracture of the femur and general contusions as the result of a fall from a ladder in his store. At the time of his accident he was arranging stock on the shelves. He had a delirious reaction following the application of a cast and a stormy hospital course. Two years after the injury he was a prematurely aged man, complaining of backaches and pains in his leg, unable to return to work, irascible with his wife and bitterly resigned to dependence on the bounty of a younger brother.

This patient was the oldest of three boys. For financial reasons he had been unable to continue his education beyond high school. This had been a severe disappointment. He had worked hard and helped support his family. At age 28, he had married. It had been his ambition to establish himself in business but various vicissitudes delayed this. Finally, he had succeeded only to lose his investment during the depression. Subsequently there had been years of poverty until the outbreak of the world war when he recouped his position. At the time of his accident he had been starting out for the second time in a business of his own—with this important factor operating: He was being helped to finance the venture by the next younger brother whose luck had been better.

While there are various psychic factors in this case which made it necessary for this man to injure himself and to remain ill—among them his hostile jealousy of the very brother who was helping him—it is clear that his regression to invalidism was in its comprehensive aspects a surrender to his repeated failures, despite his efforts to master the anxiety-stimuli involved in his drive for success.

Example 3. The secondary gains which are conducive to chronic invalidism generally represent opportunities to escape from life situations in

which the patient finds himself defeated or threatened by defeat. There are many complicated psychological factors operating in these cases of flight into illness which cannot be explained in the terms of the present discussion alone. However, in all of them there is the common factor of anxiety. The life situation may be characterized by actual insurmountable obstacles or by insoluble neurotic conflicts involving envy, hostility, and guilt. Whatever the case may be, the regression into invalidism serves the comprehensive purpose of protecting the person against the need of coping with the anxiety situation in its own terms.

The operation of secondary gain is well seen in the case of the constitutionally handicapped boy, cited previously. There was a specific emotional basis for his invalidism in the fact that at the preventorium he had for once in his life known what it was to be free of anxiety. To be sick really meant to him to be safe.

*Example 4.** There are patients who quite literally surrender before the impact of illness. This occurs chiefly in conditions of great seriousness. Most important and most difficult to understand is the fact that this may occur in the absence of the patient's knowledge of what exactly is wrong.

An elderly man who had sold his business preparatory to retirement to California was admitted to the hospital because of complaints of weakness, fatigue, anorexia, insomnia and cough. These symptoms had appeared after an attack of flu seven months previously. A week previously there had been an attack of pleurisy. Despite the anorexia there had been no weight loss and under observation he even gained a few pounds.

Apart from marked clubbing of the fingers the physical findings were negative. Bronchoscopy and lipiodol studies of the chest revealed nothing definite. Repeated roentgen-rays revealed widening of the superior mediastinum and an accentuation of the left hilar shadow. The roentgen-ray report stated that "early neoplastic change could not be excluded." However, the patient knew nothing of this.

Psychiatric study was requested because he had suffered from a depression 10 years previously and he was again apparently depressed. He had an attitude of complete hopelessness and appeared listless. His facial expression and bodily posture were those of apathetic surrender. He had at one time looked eagerly forward to living in California but this was now a matter of complete indifference to him. He minimized depression and emphasized his fatigue. He repeatedly stated that there must be something the matter with his chest. He had an air of anxious pleading for help but with an attitude of hopeless resignation. During office interviews, after his discharge from the hospital, he remained uncommunicative or would cry silently and murmur that he expected to die very soon.

Five months after this study, he died. In the interim weight loss had set in and weakness had become profound. Postmortem examination revealed a bronchogenic carcinoma with metastases to lymph nodes and intestines.

*Example 5.** Another case of malignant disease presented quite clearly a similar picture of passive resignation and the attitude of a hopeless plea

* I am indebted to Dr. Winston Breslin of the Division of Neuropsychiatry, Michael Reese Hospital, for the clinical histories of examples 4 and 5.

for help. A dream which this patient diffidently revealed is quite illuminating: He dreamt that he was in a house in which everything was rotting and falling to pieces.

In cases of this type illness literally delivers a knockout blow to the psychic resources of the patient.

(*B*). *Repression of Illness Anxiety.* Some patients do not permit themselves to become clearly aware of the specific anxiety tension which illness may induce.

Example 6. The classical example of this is the euphoria of some tuberculous patients. A striking instance is the following one: A psychiatric patient, whose mother suffered from chronic tuberculosis and was going downward, informed me that on the morning of the day that his mother died she talked with him cheerfully before his departure for school, about measuring him for a suit on which she planned to start work the following day.

We are all familiar with the euphoric megalomania of the paretic which masks the actual anxiety induced by the disintegration of his intellectual functions with increased pressure of intellectual activity and grandiose plans.

Example 7. A young man who had been diagnosed as having early syphilis appeared to take the information quite philosophically, only to report on his next visit the appearance of new symptoms: tachycardia and polyuria. Only a little exploration sufficed to reveal these to be connected with barely apprehended fantasies of an anxious type.

Example 8. A patient who had come into analysis because of a neurosis of some 10 years' standing complained also of fatigue. Two months after the analysis began it was suggested that he have a physical examination because of the excessive character of the fatigue. He was examined by a competent physician and was found to have pernicious anemia.

The psychologically important things about this case are the following: He had postponed the examination for a month after it was discussed with him, during which time he had depreciated the symptom and preferred to attach it to his neurosis. When the diagnosis was final he insisted that it was of small moment and that there was really nothing to worry about. He showed prompt symptomatic improvement under treatment and his conscious attitude towards his somatic illness continued to be one of optimism. However, his dreams began to deal with the topic of his feeling of helplessness and he began to have, while on the couch, intense recurrent visual fantasies in which he appeared as a frightened little boy at whom his father was shaking an admonishing finger. This man had good reason for feelings of guilt and of fear of loss of status, and his unconscious reaction to his somatic illness was governed by those feelings.

(*C*). *Flight into Health*—Denial of Anxiety. This brings us to the situation in which anxiety may lead to reactions against itself. In part, the last case described is an example of this. But there are the striking cases in which the patients are even more overt in their denial of the anxiety connected with illness.

Example 9. A man of 50 suffered from a coronary attack. Instead of following the regime advised by his doctors he pooh-poohed their caution and hastened his death by transferring his business to his bedside. This patient was one of those persons who never delegated authority. He had never been able to depend on others and in the end could not allow himself even a temporary regression into the dependency of illness.

Example 10. A male patient in his forties was admitted to the hospital for study because of loss of weight, mild anemia, and the occasional appearance of occult blood in the stools. Carcinoma of the gastrointestinal tract was suspected ***but he had not been informed of this.*** In the hospital he gave trouble with his complaints about the food, about the nursing service, about everything. He denied the validity of his hospitalization and insisted on going home.

During the psychiatric examination he was responsive, coöperative, apparently cheerful. He gave a coherent life story which did not reveal any unusual neurotic traits and there was no evidence of current stress in his life situation. However, there was one discrepancy. Since his admission to the hospital he had been having catastrophic dreams. Their content was vague—he only knew that they were distressingly fearsome. He continued to deny the necessity for hospitalization and finally left against advice before a diagnosis could be made.

Three weeks later he was brought back to the hospital in coma and died within 24 hours. Postmortem examination revealed a carcinoma of the stomach with metastases to the brain.

In this case the question may occur as to whether or not the patient's reaction may have been due in the first instance to the fact that he had organic disease of the brain with consequent impairment. It must be emphasized that there was no clinical evidence of an organic type of cerebral reaction at the time that he was examined, and that in any case the reaction of the patient would have encompassed this aspect of the threat to his total organic integrity.

Example 11. A chronically neurotic woman of 40 who lived in masochistic submission to a husband whom she hated, was admitted to the surgical service because of weakness, loss of weight and pain in the back which radiated into both arms. Inconstant dysphagia was present and had been interpreted as globus hystericus. In the clinic examination the only positive finding had been cholelithiasis. Because of the psychiatric history consultation was requested.

The examination revealed the old neurotic problems which had reached a pathological equilibrium. She continued to live her life as it had been at the time when she was last seen some years before. Nothing new had developed emotionally. The old hostilities and the old submissions were still in the picture. Only the somatic symptoms were new. Although she adhered to a consistent description of these new discomforts she was curiously unworried about them. Her mood was apparently good. She spoke of the old neurotic situation but without special intensity. However, while she made inquiries as to when she could go home, her attitude about this seemed quite tentative.

Further diagnostic procedures were advised and in the end a diffusely infiltrating squamous cell carcinoma of the esophagus was found. A month later she died in consequence of hemorrhage.

Cases of this type demonstrate the "flight into health."

V. Illness Anxiety and the Doctor as Magician

The history of medicine begins with the history of magic. It is unnecessary to detail the facts of this. We are all aware of the attitudes of awe, fear, hope, and veneration with which patients come to a physician's office or to a hospital. The final source of such feelings is to be found in the person's anxiety of the unknown and unpredictable powers that may govern his fate. Even the most sophisticated may turn to religion and mysticism as a final support when medicine fails. The success of quackery is dependent on the survival of such primitive emotions.

The physician is often blind to the magical implications of everything about him for the patient, from his white coat to the most imposing treatment apparatus. The doctor is the embodiment of the nursing and protecting mother and of the controlling and regulating, rewarding and punishing father. Depending on the person, the will of God, of fate, or of dark powers is implicit in the doctor's presence. Whatever augments the mystery—the instruments, the technics, the scientific jargon—augments the anxiety.

A certain amount of this is inevitable from the very nature of human beings. A great deal of it is artifact produced by the physician and his set-up. Insofar as these attitudes of patients are inevitable they are insufficiently understood and inadequately exploited in the patient's interest. Insofar as these attitudes are stimulated by the doctor they are too much disregarded or discounted.

Some patients become "experts" on their own cases as a manifestation of an intellectual effort to cope with anxiety which has been inadequately handled in rational terms by the physician. Some patients become shoppers and wind up with quacks because the physician has adhered too severely to downright rationality.

The art of medicine consists in the judicious exercise of magic and knowledge, of paternalism and maternalism. Such psychological factors as we have discussed are relevant medical data and insofar as the principles behind them are understood and consciously exploited, the art of medicine becomes a science.

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THE U. S. NAVY'S WAR RECORD WITH TETANUS TOXOID *

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IN ALL the wars of history, tetanus has been a major menace and a master killer. The adoption of tetanus toxoid prophylaxis by some of the military forces in World War II presented an opportunity to note the incidence of tetanus with and without active immunization and to some extent to compare success attained by different programs of immunization. Before the advent of tetanus antitoxin, "lock-jaw" attacked many of the wounded and killed almost all of its victims. Antitoxin prophylaxis and treatment improved the situation but, in spite of the best possible use of antitoxic serum, tetanus still occurred and, in those who developed the infection, the mortality remained high.

Of tetanus as a killer, Roddis [1] observes: "There is no way to number its victims, for vast numbers of them are among the infants of tropical areas of Africa and Asia where infection of the umbilical cord of the newborn is common and with almost a 100 per cent mortality. In countries where statistical information is available, the number of lives lost from tetanus before preventive measures were taken was very great. In World War I, the average rate for the German Army was 380 per 100,000 wounded with about 300 deaths per 100,000. On a basis of about 4,000,000 wounded this meant 12,000 deaths from tetanus alone."

In 1940, as the probability of war involving the United States steadily increased, serious consideration was given by the medical departments of both our Army and Navy to the tetanus problem and to the desirability of adopting universal and compulsory tetanus toxoid prophylaxis. But this would require the abandonment of serum (antitoxin) prophylaxis. Did we dare to do this? We knew from experience that though antitoxin did not afford the wounded perfect or complete protection it did hold tetanus within bounds. Could we about-face and go to war depending solely for protection against tetanus upon this relatively new agent, upon active, toxoid-developed immunity?

It had been well known, and in World War I it was demonstrated on a grand scale, that the value of antitoxin progressively decreased as the time interval between wounding and injection increased. That is, the more mobile the war, with combatants separated from base medical attention, the greater the incidence of and mortality from tetanus. In the air, on the ground, on and under the water the mechanization of war promised, for the

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Opinions expressed herein are those of the writer and do not necessarily represent the views of the Bureau of Medicine and Surgery, Navy Department.

coming strife, greater dispersion of personnel and more independent action of combatants. In this respect, in World War II, reality was to far outrun expectation in air combat and in mountain, jungle and island warfare.

The adoption of tetanus toxoid by Army and Navy followed the meeting of an unofficial conference group under the Division of Medical Sciences of the National Research Council. Representatives of the Navy, the Public Health Service, the National Research Council and the Army composed this conference group. A number of the group favored the use of plain toxoid, largely because experience with this product in France and England had been satisfactory. It was felt, too, that reactions were more apt to occur with the alum than the plain toxoid. Navy experience, however, indicated the safety of both products in man and, in a few experiments with sensitized guinea pigs, it had been demonstrated that a specimen of fluid toxoid, which contained a sensitizing protein, produced fatal anaphylaxis, while protein containing alum precipitated toxoid could be injected without reaction. We [2] had reported fairly extensive and very satisfactory results using alum precipitated tetanus toxoid. The largest group immunized with alum precipitated tetanus toxoid had been the midshipmen at the naval academy where all members of the academy had been so treated. Our serological examinations of these men,[2] and other volunteers on the U. S. S. RELIEF, where the work first began,[3] in 1934, had revealed no individual who had failed to respond satisfactorily with the development of antitoxin to the injection of either fluid or alum precipitated tetanus toxoid. However, the alum toxoid had proved a much more potent antigen and had given higher serum antitoxin titers over a longer period of time. Satisfactory immunity had been developed routinely by the means of two injections of alum precipitated tetanus toxoid at one to two month intervals whereas three injections of plain toxoid at shorter intervals were required. In fact, the principle of secondary stimulation from the depot of slowly soluble alum toxoid produced a rising curve of antitoxin for about a month and reached a level, with only one injection, which probably represented a safe protective initial immunity. This seemed to be a most desirable situation to be in, when, with men by the many thousands being rushed through the training camps, clerical or technical error might cause one of the two prescribed injections to be missed.

It was, therefore, decided to adopt alum precipitated tetanus toxoid as the immunizing agent for the Navy and the Marine Corps, while the Army adopted the plain or fluid toxoid.

At first, some of our medical officers were hard to convince. Doctors are traditionally individualists and many are conservatively inclined to hold to the old method which they know to be good rather than to depend upon the new procedure which, experimental evidence and field observations not withstanding, they feel may or may not be better. For example, one of our surgeons handling a considerable number of cases, at the time of the Pearl

Harbor attacks, refused to depend upon toxoid immunization, though service wide active immunization under Bureau directive had been completed at that time.* He gave every one of his cases antitoxin. Such attitudes soon melted away in the heat and pressure of war activity.

Table 1 gives by years the peace time strength of the Navy and Marine Corps—1919 to 1941—with the number of accidental wounds reported each year, the cases of tetanus diagnosed and the deaths. Personnel for those 23 years averaged approximately 143,000; wounds each year averaged 1400 and for the 23 years, totaled 35,840. During these years, a total of 13 cases of tetanus were reported with five deaths.

Table 2 gives average strength of the Navy by years for World War I and II with cases of tetanus and deaths and the totals of wounded for each war. In World War I, there was a total of 9,670 wounded in enemy action with two cases of tetanus and two deaths. In World War II, there were 89,988 wounded in action with four cases of tetanus and two deaths.

Examination of the medical records of the four cases of tetanus, which were verified as having been properly diagnosed as tetanus, reveals the following: All of the four were Navy personnel, no Marines having developed the infection in spite of the high percentage of Marine Corps wounded who were injured ashore in beachhead and island combat. Of the two deaths, one (designated *Case A*) died 10 days after entering the service in 1942. He reported to the training station with an infected ingrown toe nail in which

* *Immunization against Tetanus in U. S. Navy.*

Requirements:

General: All personnel of the Navy and Marine Corps on active duty, regardless of age, shall be immunized against tetanus. Alum-precipitated (insoluble) toxoid shall be used.
Initial Immunization: Initial immunization shall consist of two injections of 0.5 c.c. each given intramuscularly at an interval of not less than four and not more than eight weeks. Such injections shall be given to all personnel as soon as practicable after entrance into service.
Booster Immunization: One year after the completion of the initial immunization, all personnel shall be given, intramuscularly, a single booster injection of 0.5 c.c. of alum-precipitated tetanus toxoid. Thereafter a single booster injection shall be given every four years in the event no emergency booster injections have been recorded during the interim. In addition to the above, all personnel shall receive, when possible, booster injections of 0.5 c.c. of alum-precipitated tetanus toxoid before going into combat zone, preferably one month prior to entrance into the zone.
Emergency Booster Injections: In addition to the initial and routine booster injections, emergency booster immunization, consisting of 0.5 c.c. of alum-precipitated tetanus toxoid, given intramuscularly, shall be administered immediately under the following conditions: (a) whenever an individual receives a wound or severe burn in battle, (b) whenever a patient undergoes a secondary operation or open manipulation, if, in the opinion of the medical officer, there exists the possibility of contamination with tetanus spores or organisms, and (c) whenever an individual receives punctured or lacerated non-battle wounds, powder burns, or other conditions which might be complicated by the introduction of tetanus spores or bacilli.

Precautions: When administering tetanus toxoid, especial care shall be exercised (1) to assure that the injections are deep and given intramuscularly; and (2) to avoid injecting tetanus toxoid directly into the blood stream. The preferred site of injection is the deltoid muscle, approximately half the distance from the point of the shoulder to the insertion of this muscle. Due consideration shall be given to the possibility of a sensitivity reaction.

TABLE I

Tetanus Cases and Deaths
1919–1941
U. S. Navy *

Year	Average Strength	Cases	Deaths	Total Wounds (Cases)
1919	298,774	3	2	2,850
1920	140,773	0	0	1,552
1921	148,861	2	1	1,574
1922	122,126	0	0	1,384
1923	116,565	0	0	1,308
1924	119,280	3	2	1,274
1925	115,391	1	0	1,407
1926	113,756	0	0	1,413
1927	115,316	0	0	1,438
1928	116,047	0	0	1,332
1929	117,388	0	0	1,391
1930	117,453	1	0	1,489
1931	112,767	1	0	1,444
1932	110,717	1	0	1,461
1933	108,183	0	0	1,442
1934	109,383	0	0	1,438
1935	114,188	1	0	1,423
1936	124,408	0	0	1,420
1937	132,855	0	0	1,484
1938	139,216	0	0	1,316
1939	149,618	0	0	1,331
1940	202,614	0	0	1,704
1941	348,926	0	0	2,965
Total		13	5	35,840

* Includes Marine Corps—Source: Surgeon General's Annual Reports.

TABLE II

Tetanus—U. S. Navy *
World War I and World War II by years

Year	Average Strength	Total Cases	Deaths	Total Admissions for Wounds
1917	245,580	0	0	World War I
1918	503,792	2	2	9,670**
Total		2	2	
1942	834,639	2(A)(C)	1(A)	
1943	2,108,379	1(B)	1(B)	World War II
1944	3,349,798	0	0	89,988**
1945	3,673,855	1(D)	0	
Total		4	2	

(A) Existed prior to enlistment.
(B) Immunization record incomplete and unsigned, probably received neither basic nor booster injections.
(C) Received basic immunization but no booster injection.
(D) Fully immunized.
* Includes Marine Corps—Source: Surgeon General's Annual Reports.
** Include only wounds resulting from enemy action.
See footnote on page 302.

tetanus developed; he was given a total of 200,000 units of tetanus antitoxin. He died two days after the disease was recognized, 10 days after entering the service. Tissue was removed from the infected toe and tetanus bacteriologically verified. This case was recorded as having contracted his infection prior to enlistment (EPTE) and was not considered as a failure of toxoid immunization. *Case B*, who developed tetanus and died in 1943, sustained a compound fracture of the leg when he fell from a window. Tetanus was recognized clinically seven days after the accident. Large amounts of tetanus antitoxin were given but the patient became rapidly worse and died in a few days. Examination of his immunization record revealed an incomplete entry of two injections of alum-precipitated tetanus toxoid earlier in the year, not signed by the medical officer. At the time of injury, booster injection was noted as "ordered" but not recorded as having been given. This case was not accepted as tetanus in an immunized individual, there being doubt that he received any toxoid at all, basic or booster. *Case C* developed tetanus in 1942 after he had sustained a crushing injury of the legs and feet. Gangrene resulted with later amputation of left leg and toes of right foot. Tetanus developed in a mild or chronic form about one month after injury. The disease was successfully treated with tetanus antitoxin. Immunization record indicated that he had received two basic injections of alum precipitated tetanus toxoid but that he had not received a booster injection of toxoid when injured nor at any time subsequently. Time of onset and course of the tetanus infection suggest partial protection from the original immunization. Because no booster injection was given, this case is not accepted as a failure in a fully immunized case. *Case D* was admitted in 1945 with a crush injury left great toe. Symptoms of tetanus developed eight days later, with recovery in 10 days under antitoxin therapy. Immunization record in this case indicated that the two basic immunizing injections had been given in 1943, an annual booster injection in 1944 and a booster injection given after injury. Clearly, this was a case in which active immunization failed fully to protect. The mildness of the infection and rapid recovery may possibly be accepted as indicating partial protection. Summarizing the above, we have one nonfatal case of tetanus in a fully immunized man; one nonfatal case of tetanus in a man who had received the basic immunization but not the emergency booster injection; one fatal case of tetanus in a man who had received no immunization and one fatal case of tetanus in a man whose record is incomplete and who probably received no toxoid. It is worthy of note that none of these four cases were combat casualties.*

* (1) The U. S. Navy Surgeon General's annual report of 1943 lists cases of tetanus as 7. This error was discovered too late for correction and was due to the statistical tabulation of cases of "trismus," resulting from molar tooth extraction, as tetanus. The USPHS Manual is used in coding for illness. The Statistical Division Editor, using this as a guide, placed trismus under the diagnosis number of tetanus. (2) Case B, though occurring in 1943, is not listed in this annual report as a death due to tetanus since the report provides only the principal or primary cause of death. According to "Joint Causes of Death" case B is recorded—Cause of Death, Primary: Fracture Compound; Cause of Death, Secondary: Tetanus.

Reactions experienced in the use of alum precipitated tetanus toxoid have been minor in nature and relatively very few in number. When precautions regarding placement of the injection intramuscularly in the center of the deltoid have been followed, skin irritation has been avoided and only minor soreness of the muscle has been the rule. Alum precipitated tetanus toxoid has proved to be a most safe and satisfactory immunizing agent.

In theory, there are at least three reasons for possible failure of active immunization fully to protect against tetanus. The first is the inability or failure of the individual's immune mechanism to react. That such failure does occur in various immune processes has been demonstrated by animal and human experimental observations and in the clinical field. That such failure to react to properly administered alum precipitated tetanus toxoid is a very rare occurrence seems to be demonstrated by our experimental serological results [2] in which no individual failed to react with a titratable antitoxin response to basic immunization or to react with a prompt rise in titer to a booster or challenge dose of toxoid, even though the booster was given when the circulating antitoxin had fallen to a hardly detectable level two years or more after original injection. Such field experience as reported above, where tetanus was almost eliminated, serves even more clearly to indicate a highly uniform and reliable response. "The proof of the pudding is in the eating." The second reason for possible failure is sudden flooding of the body with high potency toxin from a massive and virulent infection. A third reason for failure might be suppression of an immune response to a challenge dose of toxoid or toxin. Toxemia or severe malnutrition might conceivably operate in this manner even though the original immune response had been satisfactory.

Some effort has been made to establish an arbitrary serum antitoxin level [4] which could be considered a safe protective level. Undoubtedly of greater importance is the ability of the individual's immune mechanism promptly to respond to toxoid or toxin stimulation.

In the discussions of tetanus during World War I and World War II,[5] it has frequently been emphasized that in a highly fertilized farming area, where herbivorous animal excreta laden with the spores of *Cl. tetani* enriches the ground, combat is followed by more tetanus from soil contamination of wounds than warfare in nonarable regions. The unsavory records of World War II tetanus, in the German troops fighting in Europe, and of the Japanese forces engaged in Pacific island warfare, demonstrate the fact that tetanus spores were everywhere that our men fought and that freedom from tetanus depended upon immunity and not upon lack of infecting organisms.

A vignette of tetanus among the Japanese casualties was given in 1944 by Comdr. H. J. Cokely, (MC) USN,[6] as follows: "During a recent evacuation of patients by this vessel from the combat zone, we embarked 284 Japanese wounded. We found them to be generally dirty, emaciated and with wounds that had been improperly treated. This, no doubt, was due to the

nature of the campaign. The main point of interest, however, was the presence of a large number of cases presenting symptoms of tetanus.

"I would consider a more formal report of the course, treatment and results in these cases had adequate records been kept. This was impossible owing to the large census on that particular trip with the resultant overload on personnel.

"From what we can gather, the Japanese troops are not routinely immunized against tetanus on their induction into service. Such immunization is reserved as a procedure to be carried out on their arrival in the combat area. As a result, many of their troops do not receive the benefit of this valuable measure.

"The incidence of symptoms of tetanus in Japanese wounded was 4.93 per cent. The mortality rate of those with tetanus during the period that they were on this vessel was 71.43 per cent.

"Faced with this large number of cases of tetanus, we found our supply of tetanus antitoxin inadequate. It was, however, spread around and utilized in those cases where the outlook appeared favorable. Having a plentiful supply of penicillin aboard, each case received 25,000 units intramuscularly every three hours. This seemed beneficial in some cases while in others the clinical picture progressed from trismus to generalized spasms, opisthotonos and death. Some, who were alive when transferred from the ship, were in none too good condition.

"For a control we had at that time 384 wounded of our forces aboard. These troops were engaged and wounded in the same area as were the Japanese. All of our casualties had been immunized against tetanus and had in the main received booster injections of the toxoid prior to action. They had, without exception, received an additional 0.5 c.c. of tetanus toxoid following their injury. There was no incidence of tetanus in our troops.

"To me this is a very valuable lesson and direct evidence of the efficacy of immunization against tetanus and will be of interest to those medical officers who, day after day, week in and week out, immunize the many thousands of our military personnel. Certainly this widespread program of protection against tetanus is now paying dividends."

Roddis[1] reports: "In the attack on Saipan an opportunity was afforded of seeing the contrast between Japanese wounded of the Imperial Army who had received tetanus toxoid and members of labor groups largely unvaccinated. Among the latter there were nearly 15 per cent of deaths from tetanus and not one from the former. Apply such a death rate to hundreds of thousands of wounded and one gets a graphic picture of the lives saved by the use of tetanus toxoid as an immunizing agent."

Tetanus in the German forces has not been officially reported and perhaps will not be. However, numerous U. S. Army and Navy Medical Officers have reported that tetanus was rife among the German wounded in their hospitals and in the wounded prisoners in ours and that the mortality was

high.[7, 8] Information gleaned by Alvis[9] while attached to the Naval Technical Unit Europe indicated that only the paratroopers of the Luftwaffe were routinely immunized. The paratroopers were given active immunization because it was believed that they might not have medical attention readily accessible so that passive immunization could be given promptly. It is reported that only four cases of tetanus developed with one death in the combined paratroop activities.

The record of protection against tetanus in the British forces is a mixed one. Not all of the troops under the British flag were actively immunized and in some of those immunized the protection was not considered satisfactory by the medical authorities, due to the fact that early in the war numbers of men had to be let go with but two injections of fluid toxoid when a standard course was determined as three injections. Boyd[5] reports 22 cases of tetanus in the British forces among those actively immunized, with 11 deaths, a 50 per cent mortality. Eleven of these 22 cases had also received prophylactic antitetanic serum (ATS), while 11 cases had not received ATS. The deaths in the group receiving ATS as well as toxoid immunization were 2 or 18.2 per cent mortality and in that group which had only active immunization the deaths were 9 or 87.8 per cent mortality. Additional figures in cases not actively immunized are given as follows: Not actively immunized but given prophylactic ATS—23 cases, 10 deaths, mortality 43.8 per cent; not actively immunized, no prophylactic ATS—39 cases, 19 deaths, mortality 48.7 per cent. Further, there were 18 cases of tetanus in which active immunization was incomplete or doubtful, three of these received prophylactic ATS and two died, a mortality of 66.6 per cent while 15 received no ATS, prophylactically with five deaths, a mortality of 33.3 per cent.

Boyd[5] feels that the failures in active immunization, 22 cases, may be attributed to "(a) Massive infection in which the amount of the toxin secreted overwhelms the blood antibody level produced by active immunization: (b) to a defective response to active immunization resulting in an antitoxin level below that required to neutralise the average infection—out of 22 cases, the failure in 6 may be attributable to the former cause. In the other 14, however, lack of protection could be explained only by the existence of an inadequate level of preformed antitoxin. To meet with such cases, the Canadian and U. S. Army Medical Officers give to each wounded soldier 1 c.c.-toxoid so as to stimulate early antitoxin production. The British Army Medical Officers prefer to give a single dose of 3000 units antitoxin in order to increase immediately the antitoxic content of the blood above the critical level." Boyd recommends the latter procedure as he feels it affords protection to poor or non-reactors to active immunization.

In comparing the mortality in the completely and incompletely toxoid immunized British, who also received antitetanic serum, with the mortality in those actively immunized, who had not received ATS, and further comparing these mortality figures with the mortality in nonimmunized cases who

had or had not received prophylactic ATS, it should be remembered that large numbers are required to balance the effect of unknown variables such as virulence of infection, nature and size of wound and to render the results statistically highly significant. However, on a purely theoretical basis it has seemed to us that the presence of ample exogenous antitoxin might prevent toxin, produced in an infected wound, from stimulating endogenous antitoxin production. That is, antagonism rather than synergism may result and the active process for the time being be suppressed. Where fluid or plain toxoid is used, the antitoxin probably persists in the tissues longer than does the toxoid. Alum precipitated toxoid, on the other hand, is released more slowly, has been demonstrated [3] to produce a rising curve of antitoxin in the blood for at least a month and presumably would outlast simultaneously injected antitoxin which disappears steadily after injection and is completely gone from the body in about two weeks.

Reports on the incidence of tetanus in the Canadian Forces where fluid or plain toxoid was used, three injections to the basic course with injury booster injection, are not now available. Unofficial information indicates that their results were quite satisfactory.

Tetanus toxoid was also used in the French, the Italian and in the Russian troops. Information on the program of injection in these forces and on their results is not now available.

In regard to tetanus in the U. S. Army in World War II, Major General Norman T. Kirk, Surgeon General reporting on the "Health of the Army" [11] says: "The record for the prevention of tetanus was especially remarkable. In spite of the many thousands of battle wounds in which tetanus has always been feared as a deadly complication, there were only five (5) deaths from tetanus during the entire war, and only two (2) of these were in soldiers who had been properly immunized." Total cases of tetanus in the Army [12] are reported as twelve (12). Analysis of the immunization status indicates that four (4) of these, two fatal and two nonfatal, had received complete immunization (basic immunization and emergency stimulating injections). Two cases, one fatal and one nonfatal, had received the basic immunization but had not received the emergency stimulating injection. Six cases, two fatal and four nonfatal, had received no immunization.

Summary

1. The use of alum precipitated tetanus toxoid in immunization of Navy and Marine Corps personnel during World War II resulted in the almost complete elimination of tetanus.

2. No combat casualties developed tetanus. However, tetanus developed in four cases of accidental injury.

3. One nonfatal case (Case D), fully toxoid immunized, developed tetanus; recovered in 10 days under antitoxin.

4. One fatal case (Case A) had no immunization; entered the service with the infection and died in 10 days.

5. One fatal case (Case B) probably received no immunization. Immunization record incomplete.

6. One nonfatal case (Case C) who had received basic immunization but no emergency booster injection developed mild tetanus one month after injury.

7. Tetanus with high mortality occurred in nonimmunized German and Japanese at the same terrific rate that the history of tetanus in previous wars had taught us to expect.

8. The British record, reported by Boyd,[5] using antitoxin prophylactically at the time of injury, in men previously toxoid immunized, is quoted. We believe that antitetanic serum given prophylactically in the actively immunized presents no advantage. In fact, it seems that when fluid toxoid is used antagonism rather than synergism between the two protective mechanisms may result during the entire time that toxoid is present in the body and the process of formation of endogenous antitoxin may be suppressed by the presence of the exogenous antibodies.

9. The excellent record of the U. S. Army using plain or fluid toxoid is quoted.

Conclusions

1. Complete dependence upon active immunization alone for protection against tetanus is fully justified.

2. Both plain and alum precipitated tetanus toxoids are excellent antigens. Alum precipitated tetanus toxoid is preferred because (a) a higher level of antitoxin response results from the alum precipitated toxoid, and (b) two injections of the alum precipitated toxoid are ample for satisfactory immunization while three of the fluid toxoid are required.

I wish to express my appreciation for the generous assistance of Captain O. L. Burton, (MC) USN, Chief of the Division of Preventive Medicine, and of Lt. Cdr. Byron D. Casteel, (MC) USN, in charge of the Communicable Disease Section of that Division, in connection with the preparation of the statistical data and the case records herein reported.

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RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE OF RECENT YEARS

(Ninth Rheumatism Review) *

Part II

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PART II

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Alkaptonuria; Ochronosis; Ochronotic Arthritis (Osteoarthritis Alkaptonuria)

Alkaptonuria represents the presence in urine of alkapton bodies, aromatic compounds which on oxidation or the addition of certain chemicals produce dark urine. The alkapton bodies consist of (1) homogentisic acid, the most common, (2) melanin, less common, or (3) aromatic compounds related to the external use of phenol—not encountered since 1933. Alkaptonuria may produce no symptoms or signs but in severe or long-standing cases the presence of the alkapton bodies in circulating blood may produce ochronosis—pigmentation of certain bodily tissues chiefly cartilages of ears, nose and joints, sclerae, cornea and sometimes skin. Ochronosis in turn may be symptomless but in time the ochronotic deposits in joint cartilages produce extensive degeneration which may result in a special form of arthritis—"ochronotic or alkaptonuric osteoarthritis."

Clinical Data. Alkaptonuria is relatively rare; about 200 cases have been reported to date.[1640, 1761] Ochronosis is even more rare: 82 cases had been collected up to 1942.[871, 1640] Eleven new cases of alkaptonuria (seven with ochronosis; nine with arthritis) were reported.[3, 409, 836, 1080, 1399, 1640, 1761, 1982] Homogentisic acid was present in five cases; both homogentisic acid and melanin in one case.[1761] In the remaining five cases the alkapton bodies were not identified. "Ocular ochronosis," pigmentation of sclerae or cornea, was present in seven of the 11 cases. An excellent review of ocular ochronosis, with an extensive review of the literature and excellent color plates, was made by Smith.[1640]

Ochronosis and arthritis were absent in two alkaptonuric children (Abbott, Mandeville and Rein[3]). Ochronotic arthritis was present in the other nine new cases of alkaptonuria. Joints most often affected were spine, shoulders, knees, hips. Ochronitic arthritis objectively and clinically resembles somewhat rheumatoid arthritis but roentgenographically it resembles osteoarthritis, but of a special and rather characteristic type. The arthritis is chronic with occasional acute exacerbations and synovial effusions. Certain of the new cases were of special interest: the first case of ochronosis with prostatic calculi removed surgically was reported by Young[1982]: homogentisic acid was found in urine and in synovial fluid. The first case in which both homogentisic acid and melanuria were noted was reported by Swirsky.[1761] In this case there appeared to be a definite chemical relationship between the articular symptoms and the amounts of homogentisic acid in urine: when disease in the joints flared up, the urinary acid seemed to be increased. The first case of alkaptonuria with hyperuricemia was reported by Leslie: in this patient, a woman 24 years old, visible ochronosis was absent but severe arthritis was present. It was chronic with acute exacerbations incompletely relieved by colchicine. Gout was presumably not present. Strangely, when colchicine was given the blood uric acid rose from 8.6 and 7.9 to 13.3 mg. per 100 c.c., "probably because of mobilization."

[Colchicine does not mobilize uric acid. Could the metabolic abnormalities present in this case have produced a false color reaction for uric acid? It would be interesting to apply the uricase method in this case.—Ed.]

Roentgenograms. Roentgenographic features are unusual and in spine so characteristic as to be almost pathognomonic. They consist of marked thinning and calcification of intervertebral disks sometimes with exostoses or ligamentous calcification. Affected shoulders reveal unusual thinning of articular space and large exostoses.[836, 1399]

[One of us, P. S. H., has seen three cases; the spinal roentgenograms were so striking and individualistic that he would agree with others [1399] that to one aware of the roentgenographic picture, the diagnosis of ochronotic spondylitis could be made or at least strongly suspected, on this basis alone.—Ed.]

Laboratory Data. A method for the instantaneous diagnosis of alkaptonuria on a single drop of urine was reported [560, 684]: a drop of alkalinized urine placed on regular sensitized photographic paper instantly turns the paper black.

Pathology. Ochronotic cartilage was described on biopsy of one joint (Hertzberg [836]).

Etiology and Pathogenesis. Theories were reviewed.[1080, 1399, 1640, 1761] No new ideas were offered. Presumably the amino acids, tyrosine and phenylalanine, are metabolized normally to produce homogentisic acid which, in cases of alkaptonuria, is not metabolized further but appears in blood and urine instead of being acted on by an enzyme or catalyst to produce acetone as in normal persons. Presumably patients who have alkaptonuria lack an essential enzyme. Ochronosis develops in about 50 per cent of cases of alkaptonuria and in most cases ochronotic arthritis develops in time.[1399]

[Seeing such cases in which a pigmenting "irritant" hastens cartilage degeneration resulting in a special osteoarthritis, one wonders whether the analogy could be applied to primary osteoarthritis in which a nonpigmenting chemical irritant might be operating rather than a simple mechanism of ordinary wear and tear.—Ed.]

Treatment. Various methods, mostly of uncertain merit, were discussed (Leslie [1080]): liver extract, ascorbic acid, vitamins C and E. Use of salicylates or aminopyrine decreased urinary homogentisic acid and relieved articular symptoms in one case (Swirsky [1761]).

Gaucher's Disease Affecting Bones and Joints

This rare familial disorder of lipoid metabolism is characterized by deposition of kerasin in reticular cells of the reticuloendothelial system. Infiltration of bony trabeculae by Gaucher's cells eventually produces mottling as seen in roentgenograms. Involvement of femoral heads may produce osteoarthritic lesions suggesting Legg-Calvé-Perthes' disease; to 16 such cases previously reported in the literature eight cases were added (Schein and Arkin). In one case the disease began as an "arthritis" of many joints of a child. Diagnosis was made after puncture of sternal bone marrow.

Another case presented unusual features which included scattered ecchymoses, recurrent migratory polyarthritis "not unlike rheumatic fever," spindling of finger joints, narrowing of articular spaces in roentgenograms, osseous abnormalities including multiple cystic changes especially in femoral heads. Biopsy of humerus revealed Gaucher's cells (Reed and Sosman).

Psoriatic Arthritis

Incidence. It is generally agreed that the association of arthritis of the rheumatoid type with psoriasis is significant and not merely the coincidental occurrence of two rather common diseases. Psoriasis was present in 2.7 per cent of 300 unselected patients with rheumatoid arthritis, in only 0.7 per cent

of a similar number of nonarthritic controls.[90] The incidence of arthritis "of one form or another" in cases of psoriasis was reported as 12 [1315] and 15 per cent.[282] The incidence of "arthritis" among psoriatics varied from 0.2 to 25 per cent according to others.[896]

Clinical Data. Exacerbations and remissions of joint manifestations synchronous with those of nails were again noted.[90, 1402] Diagnostic emphasis was placed on the involvement of terminal phalangeal joints in association with nail lesions. But arthritis confined to the terminal joints alone is not common in psoriasis and was seen in only three of 26 cases of chronic arthritis and psoriasis.[90] The remaining 23 patients had arthritis of the rheumatoid type, 17 had psoriatic nail changes of which 13 had terminal joint involvement. Bauer, Bennett and Zeller [90] preferred to restrict the term "psoriatic arthritis" to cases in which the arthritis is limited to the terminal phalangeal joints, but involvement of these joints may occur in rheumatoid arthritis.[90]

[Uncommonly.—Ed.]

Three cases of psoriatic arthritis were reported by Franks and Wallace: in two the psoriasis antedated the arthritis which appeared with a flare-up of the skin lesion. In one case the skin and articular lesions appeared almost simultaneously, the arthritis being noted " a short time" before penile psoriasis. Joints affected were fingers and feet (but not terminal joints), knees and sternoclavicular joints, giving the appearance of rheumatoid arthritis. Under treatment the joints improved "correspondingly to the improvement made by the skin" even though in one case treatment was confined to skin.

Although in most of their 26 cases of chronic arthritis with psoriasis the condition seemed to Bauer, Bennett and Zeller to resemble rheumatoid arthritis, despite the involvement of terminal phalangeal joints in 17, one of their cases was unique. A man, aged 68 years, began to have arthritis of the terminal phalangeal joints with nail changes at age 24 years. Psoriasis of scalp and umbilicus occurred at age 39 years. Terminal joints were swollen and fingers and toes had shortened. After death from coronary occlusion examination of terminal joints revealed "unusual and distinctive alterations" (marked articular destruction and bone resorption) because of which Bauer, Bennett and Zeller concluded that in rare cases "articular lesions are sufficiently unlike those of rheumatoid arthritis to suggest important differences in pathogenesis if not in etiology." Even so they admitted that such an unfamiliar joint lesion might represent a rare form of rheumatoid arthritis.

An even more unique case was reported by Jungmann and Stern as "a possible example of arthritis psoriatica." A woman, aged 51 years, had had chronic polyarthritis for 18 years; psoriasis had commenced "simultaneously with her joint trouble." Hands and fingers were childlike, rubbery and hypermobile. Hips and knees were flexed. Roentgenograms showed remarkable changes: partial or complete dissolution of certain carpals, metacarpals, phalanges, humeral heads; tapering of ulnae, metacarpals, clavicles, metatarsals; destruction and dislocation of sternoclavicular, acromioclavicular and shoulder joints; fusion of radiocarpal joint and certain vertebrae.

Pathology. The pathologic changes in the joints of six patients with arthritis and psoriasis, four of whom had involvement of terminal joints, were indistinguishable from those of uncomplicated rheumatoid arthritis.[90] But a striking difference was found in the one psoriatic patient (noted above) with arthritis confined to the terminal phalangeal joints of both fingers and toes. Marked

articular destruction and resorption of bone caused pronounced shortening of the middle phalanges. Pronounced marginal overgrowth of bone at the sites of tendon insertions in the distal phalanges had led to the formation of cuplike deformities. The diffuse osseous atrophy usually seen in rheumatoid arthritis was not present. Most of the terminal joint spaces were replaced by dense acellular fibrous tissue in which inflammatory changes were absent or minimal.

The histopathologic findings in the skin in 225 cases were reported (Burks and Montgomery).

Etiology. 1. Of the Arthritis. Two views continue to prevail: (1) that the skin lesions produce a toxin which affects joints, hence the skin disease is the cause of the arthritis (relief of joints by treating skin supports this view); (2) that both skin and joint lesions result from some agent acting on the two different organic systems and are therefore coördinated (the occasional appearance of the arthritis before the skin lesion supports this view). The first view was favored by Franks and Wallace, the second by Jungmann and Stern who suspected that psoriatic arthropathy as seen in their case might be related to that seen in "main en lorgnette" (Weigeldt, 1929 [1d-f]).

2. Of the Skin Lesion. A strong family history among psoriatic patients was again noted.[666, 844] The disease is very rare among Negroes.[1543] Evidence was presented in support of an infective etiology.[844]

Treatment. 1. Of Joints. In one case the joints cleared up apparently as a result of treatment to the skin lesions; in two other cases additional treatment for joints (physical therapy) was used.[589] In four of nine cases with psoriatic nails roentgen treatment of nails produced complete symptomatic relief of arthritis of adjacent terminal joints and in four, marked improvement.[1402]

2. Of Nails. Popp and Addington [1402] advocated roentgen therapy for psoriatic nails and arthritis of adjacent terminal joints. Radiation was applied to the dorsum of the hands or feet from the tip of the nail to the wrists or ankles. Complete remissions occurred in the nails with, as yet, no exacerbations in six of 24 cases, and marked improvement in 10 others. The results lasted from six months to as long as five years. But Saunders [1539] noted disappointing results.

3. Of Skin. Goeckerman's regimen (1933 [1a]) was favored by several.[232, 589, 1315] Other regimens were outlined.[143, 163] Results with vitamin D were conflicting.[1033, 1539, 1966] Citrin lemonade which contained vitamin P and ascorbic acid was recommended by some [666] but others noted no benefit from ascorbic acid, adrenocortical extract, a low potassium diet,[1091] or deproteinated pancreatic extract (depropanex).[482] The blood lipoid content was unaffected by use of lipocaic.[163, 1866] "Routine treatment" plus the use of soy bean-lecithin mixtures seemed to help in 15 "very resistant" cases [669] and was recommended.[710, 1636]

"Opera-Glass Hand" (La Main en Lorgnette)

The fourth case of this rare condition was reported by Crain [403] in a man, aged 55 years, who had had what was apparently chronic polyarticular rheumatoid arthritis with severe acute exacerbations for 13 years.

Features included: short stubby fingers, skin over finger joints wrinkled and folded, no ankylosis of phalangeal joints, extensive osteoporosis, resorption and partial dissolution of joints of fingers, wrists, elbows, shoulders, hips resulting in "false joints"

and "a telescopic type of subluxation." These changes in hips produced the appearance of "Otto pelvis."

The conditions presumably represented "rheumatoid arthritis engrafted upon or followed by some other disease such as hyperparathyroidism with alteration of the arthritis as is the case in psoriatic arthritis." In the original description by Marie and Leri (1913) necropsy studies revealed extensive fatty degeneration; bones were reduced to mere shells and there was no evidence of cellular activity of a reparative or destructive nature. Because joints other than hands were affected Crain [403] suggested the term "generalized absorptive arthritis." The case resembled that of Nelson (1938).[1f]

[Unfortunately no photographs of joints were included. The roentgenographic features in this case were somewhat like those in a case of hyperparathyroidism noted by Gutman, Swenson and Parsons (1934),[1b] even more like those in the cases of psoriatic arthropathy described by Jungmann and Stern, and by Schlionsky and Blake (1936).[1d] In the unique case of chronic polyarthritis with psoriasis described by Bauer, Bennett and Zeller [90] the dissolution of articular structures was associated with dense acellular fibrous tissue; no fatty degeneration of bone was noted. Similar roentgenographic features were present in Vishnevsky's cases of "deforming xanthomatous rheumatism, a new form of chronic rheumatism." Possibly there exists a pathogenetic relationship between these four conditions: "opera-glass hand" (without psoriasis), psoriatic arthropathy, the arthropathy of xanthomatous rheumatism, and that of hyperparathyroidism.—Ed.]

Hemophilic Arthritis

Sixteen cases were noted, one by Balensweig [66] and 15 by McDonald and Lozner who discussed the roentgenographic changes and their value in differential diagnosis.

Roentgenographic changes occurred in one or both knees of all, in one or both elbows in 14 of 15 cases.[1193] In general the involvement increased with age and ranged from mild changes (slightly increased periarticular density, marginal spurs) to severe changes (narrowing and irregularity of joint space with marked subchondral cyst formation). Roentgenographically acute hemophilic arthritis simulates any synovitis with distention of articular space. But chronic hemophilic arthritis is somewhat distinct roentgenographically: cystic changes are more frequent and severe in hemophilic than in rheumatoid or osteoarthritis. Tuberculous arthritis is less easy to differentiate.[1194] In Balensweig's case [66] diagnosis was based on the roentgenographic appearance, marked irregularity of tibial and femoral articular areas, cystic degeneration within femoral and tibial condyles.

Laboratory diagnosis of hemophilia was discussed.[1422] Coagulation time was decreased by lyophil human plasma,[918] rabbit thrombin given orally [1763] or human globulin given intravenously or intramuscularly.[1248]

"Allergic Arthritis"

A factor of allergy (bacterial, food, other) is suspected by some to operate in the production of several diseases which affect joints, in particular rheumatic fever, rheumatoid, tuberculous and gouty arthritis and palindromic rheumatism as noted in the appropriate sections of this review. Serum sickness and the occasional synovial reactions to sulfonamides or penicillin might, in the broader sense, be listed under the heading "allergic arthritis," but will be discussed under "Pharmaceutic Arthritis and Arthralgia." The average reader thinks of "allergic arthritis" in a narrower sense to mean an acute or subacute (possibly

a somewhat chronic) arthritis caused by a specific food or other antigen which acts like pollen to the hypersensitive. Presumably in such cases the administration of the offending antigen would provoke an articular reaction every time and the permanent removal of the antigen would allow the arthritis to disappear. Rare indeed have been the case reports truly indicative of such a type of allergic arthritis.[1d]

Turnbull [1823] again reported his belief that food allergy is a factor in many cases of "arthritis" but that in individual cases the hypersensitivity changes from year to year; the arthritic patients become immune to antigens to which they were formerly sensitive but become sensitive to others. He reported 10 cases of chronic arthritis of three months' to 10 years' duration, mostly in elderly women. When foods, to which skin tests showed them to be sensitive, were avoided, complete relief of symptoms occurred and lasted from 13 to 100 months until the patient's sensitivity changed. Sensitivity to other foods having then occurred, the arthritis returned but was again controlled by avoiding foods to which new skin tests showed new sensitivity.

[The clinical types of arthritis present were not described; the cases were just called "arthritis." The clinical descriptions were brief; no roentgenograms or photographs were shown; no laboratory data were given except on skin tests. Rheumatoid arthritis may have been present in some, osteoarthritis in others. Except for the occasional mention of return of symptoms when patients broke rules and ate the interdicted foods, no controlled provocative tests were done. The author surely knows that his views expressed since 1924, have received scant acceptance. But more convincing, appropriate evidence, such as controlled provocative tests with "before and after photography" of joints, would be viewed sympathetically.—Ed.]

Skin tests with foods were given 25 patients with "subacute or chronic rheumatism" by Vaughan.[1849] No connection between positive skin reactions and rheumatic flare-ups was found. Dietary restrictions based on skin reactions had no effect.

Having searched inconclusively for allergy in rheumatic patients, Vaughan [1849] searched for "arthritis" in 1,000 allergic persons with hay fever, urticaria, angioneurotic edema, migraine, gastrointestinal allergy or allergic dermatitis. About 20 per cent complained of "rheumatic pains, past or present": of these 206 patients 90 showed "joint pathology," 116 did not. Of the former, nine had rheumatoid arthritis, 32 osteoarthritis, 29 "combined arthritis," two traumatic and 18 unclassified arthritis. Of the 1,000 patients 27 "found that certain specified foods produced exacerbation or recurrence of rheumatic symptoms": joints were objectively negative between attacks in some, not in others. In these 27 cases the arthritis was classified thus: intermittent hydrarthrosis in four; intermittent hydrarthrosis with chronic arthritis in one; subacute rheumatoid arthritis in three; osteoarthritis in three; chronic arthritis [probably osteoarthritis—Ed.] in eight; joints objectively negative in six; joints not examined in two. One patient with recurrent attacks provoked several attacks with strawberries or raspberries although skin tests to strawberries were negative. An elderly woman with chronic "combined arthritis" noted articular flare-ups whenever she ate chocolate. When she did not eat eggs, the garden work caused "little or no discomfort"; when she did eat eggs, the trauma of this work caused "subacute flare-ups in the fingers."

Vaughan [1849] considered skin tests with food extracts unreliable; food diaries were required in half the cases to uncover the offending food. He concluded: about half of these 27 cases "appear to belong in the group which Hench and Rosenberg [818] term 'palindromic rheumatism.' It would appear that food or

inhalant allergens may be a cause of palindromic rheumatism. It does not follow that it is the only cause."

[It has not been proved that food or inhalant allergens are the cause of palindromic rheumatism.—Ed.]

Intermittent Hydrarthrosis

In most cases "intermittent hydrarthrosis" represents rheumatoid arthritis according to Ropes.[1493] In four of her five cases it occurred at the onset or during the course of rheumatoid arthritis and the cases "resembled in all respects those of idiopathic hydrarthrosis characterized by *periodic* swelling recurring at regular intervals with great precision." In one case of idiopathic hydrarthrosis of knees for 20 years, an elevated sedimentation rate, aching in other joints, and synovial thickening of a knee even between attacks developed.

"Metabolic Arthritis"

No articles appeared under this vague title.

Endocrine Arthritis

Acromegalic Arthritis. The gross and microscopic findings in joints of an acromegalic patient were reported by Waine, Bennett and Bauer. Although the degree of hypertrophic reaction of bone in most peripheral joints was striking, the process conformed essentially to the familiar pattern of marked degenerative joint disease (osteoarthritis). But in certain sites the changes appeared to be distinctive and could not be regarded as reactions to primary degeneration of cartilage. New growths of cartilage and bone appeared to indicate reactivation of cartilage growth and enhanced endochondral ossification, unphysiologic at the age of the patient, and perhaps the result of a specific hormonal stimulus.

[These findings were compatible with those of Erdheim who, in 1931, first directed attention to the relationship between pituitary tumors and a specific form of articular disease. The acromegalic spine is characterized by additional growth of vertebral bodies. Newly formed bone, more evident on anterior and lateral aspects of vertebrae, is demarcated clearly in roentgenograms.—Ed.]

"Menopausal Arthralgia or Arthritis." The confused nomenclature regarding articular symptoms experienced during the menopause was well illustrated by one author's reference to "menopause arthralgia" [900] and "menopause arthritis" [899] in two separate reports appearing simultaneously. [These reports presumably concerned the same, or a similar, group of patients. No clinical or pathologic definition of either menopausal arthritis or arthralgia was given. Symptoms were not described or differentiated from those of periarticular or intramuscular fibrositis or of osteoarthritis. To our knowledge no distinctive pathology of "menopause arthritis" has ever been demonstrated.—Ed.] "The menopause does not cause rheumatism and there is no such entity as 'menopausal arthritis.' At the change of life any of the main types of rheumatic diseases may first manifest themselves," so wrote Bach.[47] He and Freyberg stated that women with skeletal symptoms at the menopause rarely exhibit definite articular changes except mild osteoarthritis [47] [occasionally spinal osteoporosis—Ed.]. Although denying the exist-

ence of "menopause arthritis" Freyberg [605] considered "menopause arthralgia" separate from "fibrositis" [neither clinically defined—Ed.] and noted "improvement" in five (83 per cent) of six cases of "arthralgia," in only four (57 per cent) of seven cases of "fibrositis" treated with estrogenic substance. Others [47, 900] considered estrogens of value for the arthralgias of menopause.

Other Endocrines or Hormones. An interrelationship between "hypocorticoadrenalism" or hyperthyroidism and diseases of joints or muscles was suggested by Lyon [1138] who noted improvement in three patients with musculoskeletal symptoms (one unclassified, two with ankylosing spondylitis) treated with adrenal cortical extracts. [The evidence presented was not convincing.—Ed.] According to Freyberg [605] disturbances of thyroid, parathyroid or adrenals produce no specific type of arthritis and bear no direct or significant therapeutic relationship to any recognized type of acute or chronic arthritis.

Palindromic Rheumatism

A "new," rather rare, oft-recurring disease of joints was described by Hench and Rosenberg [818] under the title "palindromic rheumatism." The word "palindromic" which means "recurring" or "returning," was first used in the Hippocratic corpus in a nonspecific sense, and is defined in current Greek lexicons to mean "recurring" or "subsiding without coming to a head." Thus the term described the most obvious and characteristic feature of the condition, its frequent recurrences, attacks and retreats.

Chief features were multiple, afebrile attacks of acute or subacute arthritis and periarthritis, sometimes also para-arthritis, with pain, swelling, redness and disability usually of only one, sometimes of more than one, small or large joints of adults of either sex. Attacks appeared suddenly, developed rapidly and generally lasted only one or two days (occasionally a little longer), then disappeared completely but recurred at short or long irregularly spaced intervals. Despite the transitory presence of an acute or subacute inflammatory cellular exudate in articular tissues and cavity, little or no constitutional reaction or abnormality in laboratory tests and no significant functional, pathologic or roentgenographic residues were present even after years of disease and scores or even hundreds of attacks.

Clinical and Laboratory Data. Thirty-four cases were described in patients (19 females, 15 males) aged 13 to 68 years but usually between 20 and 40 years of age.

The disease had lasted an average of seven years: 16 to 25 years in four cases, six to 15 in 15, one to five in 10, less than one year in five but in each of these five from 10 to 130 attacks had occurred. The frequency of attacks varied from 10 in nine months to "thousands" in seven years. *Yearly* attacks numbered two to 10 in nine cases, 20 to 60 in 17, 100 to 200 in three, and 250 or more each year in five cases. Joints affected were usually only one in 85 per cent of cases, sometimes more. Favorite sites were fingers including terminal phalangeal joints, a wrist, shoulder, knee, toe or elbow; almost any joint was occasionally involved. The onset of attacks was at any hour but frequently "vesperal." Pain varied from mild to severe, sometimes requiring narcotics. Local disability was usually considerable; when a lower extremity was affected, 14 patients were temporarily bedridden. The usual duration was a few hours to three days; occasionally three to seven days.

Para-arthritis, red, tender swellings near an affected or nonaffected joint, occurred in 30 per cent of cases; finger pads were occasionally swollen and hot. In three severe cases intracutaneous or subcutaneous nodules (3 to 8 mm. in diameter) appeared, usually on hands, occasionally elsewhere; sometimes they lasted only a few days; sometimes they persisted. There was no anemia, leukocytosis or eosinophilia; there was often a relative lymphocytosis (37 to 48 per cent). Sedimentation rates were usually normal between attacks, generally but not always slightly elevated (usually 18 to 35 mm. at one hour; Westergren technic) during attacks. There was a moderate elevation of fatty acids (368 to 569 mg. per 100 c.c.) and total lipoids (448 to 884 mg. per 100 c.c.). Blood uric acid, calcium, phosphorus and phosphatase were normal. Roentgenograms of affected joints were consistently negative even in those patients who had hundreds of attacks within 15 to 25 years.

The condition was distinguished from "angioneural arthrosis" (Solis Cohen, 1913), the "allergic rheumatisms" of Kahlmeter (1939), gout and rheumatoid arthritis. Three of the patients were physicians who had long abandoned the idea that they had rheumatoid arthritis.

Pathology. Studies, limited in number, revealed: during attacks acute or subacute cellular reactions in synovial membrane, capsule or tendon sheath, sometimes fibrinopurulent synovial exudate; between attacks normal tissues; no pannus or destruction of cartilage, no follicle-like collections of lymphocytes or urates, and no eosinophilia in tissues.

Treatment. Many remedies were tried without notable results: adrenalin, ephedrine, benzedrine, ergotamine tartrate, histamine, histaminase, typhoid vaccine, removal of foci, sulfanilamide. One patient considered calcium gluconate (100 grains or 6.5 gm.) daily useful; another "adopted a baby, quit worrying and was cured."

Prognosis. End results in 27 cases (total duration of disease, 307 years) were: spontaneous cure in 15 per cent, attacks shorter or less frequent in 44, disease unchanged in 26, attacks more frequent in 11 per cent, and death from coronary disease in one case (4 per cent). There appeared to be no tendency for the disease to become continuous in any joint. The disease was a handicap to some, a nuisance to many, a cause of residual deformity or crippling in none.

Subsequent Data. Since the first report by Hench and Rosenberg 19 cases of supposed palindromic rheumatism have been reported in nine papers (Thompson [1793]; Mazer; Vaughan [1850]; Ferry; Paul and Logan; Grego and Harkins; Cain; Wingfield; Paul and Carr). Nine cases were reported in detail; 10 were merely mentioned in one report (Vaughan [1850]). Of those described in detail eight cases conformed to the criteria of Hench and Rosenberg, except that in one case sedimentation rates were higher than usual in one attack (Wingfield).

Of the nine detailed cases seven were in males, two in females, a sex ratio unlike that in rheumatoid arthritis. In the eight characteristic cases the disease had lasted from one to 32 years (one, four, five, seven, seven, 13, 30 and 32 years) without producing clinical or roentgenographic evidence of residual arthritis, during which time the patients had had from 100 to more than 1,000 attacks. Attacks lasted usually one to three days, occasionally one hour to 10 days. Usually only one joint was affected but attacks in any case were scattered. Sedimentation rates were almost always normal even during attacks. The latter were usually afebrile; temperatures of 99 and 99.2° F. were rarely noted. Para-arthritis affected two, nodules none. No biopsies were made.

One case (Paul and Logan [1352]) may have been a case of early atypical episodic rheumatoid arthritis rather than of palindromic rheumatism: there was anemia (hemoglobin, 11 gm.; erythrocytes, 3,780,000); the patient had lost 30 pounds (13.6 kg.); attacks lasted "several hours to several days" and at times several joints were afflicted simultaneously. Even so attacks continued to disappear completely according to a later report (Paul and Carr [1351]). Discussing 27 cases of supposed (recurrent) allergic arthritis Vaughan [1850] stated that in 10 the condition "fairly closely" resembled palindromic rheumatism and he concluded that food or inhalant allergens might be a chief cause of palindromic rheumatism.

[The individual cases were not described; data sufficient for an independent appraisal were lacking.—Ed.]

Nothing new on etiology was offered in these reports. An allergic factor seemed important to some [1352, 1850] but not to others.[552, 702, 1181, 1351] Emotional stress from hard work and other psychic factors were noted in several cases.[552, 1181, 1351, 1352]

Treatment was symptomatic in most cases; none was given in some. Oxyliodide (cinchophen hydroiodide) seemed useful in one case.[1352] Cinchophen was avoided by others.[552] Heat made one patient worse.[552] No results were obtained from epinephrine,[278] sulfathiazole, contramine (a sulfur compound) or salicylates.[1944] Special diets were recommended by Vaughan.[1850]

These reports have been partly responsible for the greater attention recently paid to certain cases of atypical rheumatoid arthritis the likes of which are generally not described in articles or texts. In addition to the usual form of rheumatoid arthritis (insidious onset, chronic progression with variable severity but incomplete remissions) and the less common acute or subacute febrile rheumatoid arthritis (sudden onset, acute or subacute arthritis lasting a few weeks or months; generally complete remission; the "infective arthritis" of British texts), another form is now being recognized and might be called "episodic (atypical) rheumatoid arthritis." It is characterized by many short attacks, separate or concurrent, with little or no evidence of residues at first, later usually chronicity and residues.

[Ropes and Bauer [1495] believe that most, if not all cases of palindromic rheumatism are really cases of atypical rheumatoid arthritis. One might argue that rheumatoid arthritis is a variable disease with differing patterns of severity and chronicity in this order: (1) palindromic rheumatism or "palindromic type of rheumatoid arthritis," persistently remitting completely; (2) episodic rheumatoid arthritis (episodic and completely remitting in some joints, chronic in a few, at least in time); (3) subacute febrile rheumatoid arthritis with notable remissions, and (4) ordinary chronic progressive rheumatoid arthritis. Those inclined to this view would regard palindromic rheumatism, not as a separate entity but as a (newly described) variety of atypical rheumatoid arthritis, perhaps a "forme fruste." They might prefer to speak of "the palindromic phase (or type) of rheumatoid arthritis."

The exact position of palindromic rheumatism and its relation (if any) to rheumatoid arthritis cannot be established until the cause of either or both is known. Meantime it seems worth while to study this type of articular disease and to differentiate it descriptively, not only from (ordinary) rheumatoid arthritis but also from "episodic rheumatoid arthritis." One of us, P. S. H., believes that in most cases a valid differentiation can be made rather readily. Thus: in palindromic rheumatism the attacks are anatomically scattered; para-arthritis frequently occurs, finger pads are

sometimes affected; attacks usually last only one or two days; intervals between attacks are weeks or months as a rule, and during the intervals articular and constitutional signs and symptoms are absent. Articular biopsies reveal changes not supposedly characteristic of rheumatoid arthritis. In "episodic rheumatoid arthritis" the "attacks" tend to recur in favored sites; para-arthritis is not notable; involvement of finger pads has not been seen. Some attacks tend to last longer (frequently several days, occasionally weeks) and the intervals between attacks are shorter (and often tend to become increasingly shorter) than in palindromic rheumatism. In episodic rheumatoid arthritis symptoms between attacks (mild tenderness, stiffness, slight residual thickening) are often present but are ignored or discounted by a placid patient or by a physician fearful of the correct diagnosis. Between attacks elevated sedimentation rates and constitutional symptoms are often present (anemia, loss of weight, undue fatigue) even if joints are free or relatively so. Roentgenograms of a now painless, but formerly affected, joint may be "positive," not persistently normal as in palindromic rheumatism. Finally, articular biopsies in the episodic cases may reveal changes suggestive or characteristic of rheumatoid arthritis.—Ed.]

Epidemic Tropical Acute Polyarthritis

("Fox-Hole Arthritis"; "Bougainville Rheumatism")

Historical Data. In September, 1942, a "new form" of rheumatism appeared among Australian soldiers in the Darwin-Adelaide River area of the Northern Territory of Australia. Its four chief features were acute polyarthritis, mild fever, transient rash and lymphadenopathy. At first it was thought to be rheumatic fever. Cases increased in October, and in December, 1942, it affected 24 American and five Australian soldiers in the Birdum Larrimah region of Northern Australia. These 29 patients were studied at the 135 Medical Regiment Hospital by Hidde[841] who regarded the condition as a new entity and reported it on January 29, 1943, to the Surgeon General of the United States Army. The report was a "secret paper" and not published.

The disease spread through the Northern Territory of Australia and slowly spread south to affect military units along the Darwin Tenants Creek Road. Near the end of January, 1943, the first case was reported from the Mt. Isa region, 800 miles south of the place of origin. Meanwhile cases were increasing among Australian soldiers in the Northern Territory and between November 1, 1942, and January 31, 1943, 105 patients with it were admitted to two Australian army hospitals and studied by Halliday and Horan, of the Australian Medical Corps, whose report, apparently made independently and without knowledge of Hidde's report, was published on October 9, 1943.

Another small epidemic occurred during November and December, 1943, in the Northern Territory mostly within a radius of 30 miles of the Adelaide River area. A brief summary of about 65 cases was reported by Harris.[775] In February and March, 1944, the disease spread east and appeared in Queensland; 28 cases were reported by Sibree. In March and April the disease first appeared outside Australia and affected American troops on Bougainville; no cases were reported from other South Pacific islands.[533]

In the Bougainville epidemic (March to May, 1944) about 124 American and a few Fiji soldiers were affected; Negro troops were unaffected. At the Twenty-First Evacuation Hospital 41 cases were analyzed by Mulvey[1270] and McCarry.[535] That fall (October) the disease reappeared, this time in the Oro Bay area near Buna in New Guinea where 20 or more American soldiers were affected.[536]

The soldiers had nicknamed their disease "fox-hole arthritis" or "Bougainville

rheumatism." Terms used in medical reports were "acute polyarthritis," [742, 841, 1605] "polyarthritis," [775] "acute arthritis," [1270] "acute polyarthritis with eruption." [536]

[The term "epidemic tropical arthritis" was recently suggested by one of us, D. C. C.; perhaps the term "epidemic tropical acute polyarthritis" would be even more suitable.—P. S. H.]

Clinical Data. A total of more than 371 cases were noted in these seven reports. Except for minor variations, the clinical features of all cases were similar.

Of gradual onset, initial symptoms were pains, sometimes redness and swelling, of many peripheral joints. Involvement of midphalangeal joints of fingers sometimes resembled acute rheumatoid arthritis. Usually following, but sometimes preceding the acute polyarthritis was a maculopapular rash somewhat resembling rubella or chickenpox. Rupture of vesicles or desquamation did not occur. Tender enlargement of lymph nodes and a mild fever (99° to 101° F.) were present. In most cases the conditions cleared completely within 10 to 20 days. No residual cardiac or articular damage resulted.

Etiology. This was not determined. Facilities for intensive studies on etiology were lacking in American field hospitals. But agglutination tests with Proteus OX19, XK and OX2 strains and for *Brucella abortus* were negative (Halliday and Horan; Hidde). Halliday and Horan reported cultures of blood, joint fluid, urine, stools and tonsils to have been negative. The seasonal periodicity of the epidemics was of interest. It appeared each year for three successive years with the onset of the hot season and stopped abruptly with the onset of heavy rains. [The rainy season starts in November and is marked in January and February.—Ed.] This suggested the factor of an insect vector but no proof was found. The disease is probably endemic in the Northern Territory but its occurrence has gone unnoticed because the peacetime population was small.

Differentiation. Considered were rheumatic fever, Haverhill fever and dengue. No streptococcic pharyngitis preceded the disease; response to salicylates was poor. The rash was more extensive than that seen in dengue; pains were articular, not osseous and the postdengue exhaustion was absent.

Treatment. Symptomatic treatment was employed.

Reiter's Syndrome (Urethritis, Conjunctivitis, Arthritis)

The first report in the English literature on this clinical syndrome [except for a reprint from a German article by Fruehwald—Ed.] was based on six cases observed by Bauer and Engleman and a review of 20 authentic cases reported in foreign literature. The clinical course of this syndrome of unknown etiology is characterized by urethritis, purulent conjunctivitis and arthritis (and at times, diarrhea). Ten cases were observed subsequently among personnel at a naval station (Rosenblum) and 25 cases were reported from an army rheumatism center (Hollander, Fogarty Abrams and Kydd). [In many of the latter cases the triad of symptoms were not present and, therefore, they should not have been included as cases of Reiter's syndrome.—Ed.] Other cases were noted among military personnel and civilians.[115, 357, 627, 1081, 1129, 1240, 1735]

Affected have been young men, aged 20 to 30 years. Usually purulent urethritis, but sometimes conjunctivitis, marks the onset of the disease. Urinary and ocular

symptoms are generally short-lived. The arthritis is persistent and disabling, involving several weight-bearing joints most frequently, though monarthritis does occur. Constitutional symptoms are usually mild. The disease runs a self-limited course; attacks last one to five months. Recurrences months or years later occur in 25 per cent of cases and may involve any or all of the three systems.[91] Renal complications may occur [1240]; pyelonephritis affected a kidney removed for hydronephrosis.[357] Skin lesions resembling erythema multiforme [1504] and keratosis blenorrhagica [1081] have been reported as features of Reiter's syndrome, and Reiter's disease was considered identical with "nongonorrheal keratosis blenorrhagica" by some.[1129] [Important deviations from the accepted clinical picture make one question the diagnosis.—Ed.] The association of diarrhea with the usual triad of arthritis, conjunctivitis and urethritis was commented on [91, 858] and led one author to the unproved conclusion that "Reiter's disease appears to be nothing more than the familiar dysenteric polyarthritis with superadded toxic manifestations." [115]

Synovial fluid examinations showed alterations observed in the specific arthritides.[91] Bacteriologic examinations of urethral, prostatic and conjunctival exudates, and synovial fluids were negative for gonococci; urine and blood cultures have been sterile.[91] Biopsy of a joint during the acute phase revealed markedly injected synovial membrane with intense hyperemia and small focal areas of acute inflammatory cellular infiltration (Bauer and Engleman). The roentgenograms showed bone atrophy of varying degree and, rarely, circumscribed areas of subchondral atrophy.

The etiology is unknown. The possibility of a staphylococcic etiology was suggested without adequate evidence.[637] The allergic and toxic theories [115, 637] also were unsubstantiated. Bauer and Engleman [91] favored an infectious origin, although they did not demonstrate the agent. [Subsequent studies being done by one of us, W. B., and his colleagues (Dienes and Smith [468, 469]) suggest that pleuropneumonia-like organisms may be related to Reiter's syndrome.—Ed.]

Treatment with sulfonamides and penicillin was without benefit.[91, 858, 1240, 1504] Induction of febrile reactions by intragluteal injection of boiled milk [1735] and "arthrigon" [115] presumably resulted in marked clinical improvement. [Evidence to substantiate the value of such treatment is lacking.—Ed.]

[This is another example of the confusion that may arise if an eponymic designation becomes attached prematurely to an original incomplete clinical description. In 1916 Reiter reported one case of diarrhea, acute urethritis, conjunctivitis and arthritis in a young army officer; reportedly cultured from the blood was a spirochete (forans) not found in controls. Mice infected with the spirochete developed an acute illness with marked sweating but apparently no articular, ocular or intestinal lesions. The patient also had sweat considerably. On this evidence Reiter concluded that the spirochete caused the patient's disease which he named "spirochetosis arthritica." Twenty-five years later (1941) Reiter saw fit to report again the same original case with no additions whatever. Meanwhile European writers had described under various titles, especially "Reiter's disease," cases in which variable clinical features were present. Most of these have been rejected by Bauer and Engleman [91] as not representing the syndrome. In general the diarrhea of Reiter's quadriad was not included and reports spoke of the "classical triad." A spirochetal origin was not confirmed.

Current American reports have likewise been confusing: there has been no agreement as to the clinical content, as to whether the arthritis is acute or subacute with complete remissions or progressively chronic with destructive residues, roentgenographically similar to rheumatoid arthritis. Some writers insisted that any one or even two features of the "classical triad" may be absent; others have reported as

Reiter's disease cases of chronic arthritis with skin lesions and without urethritis, conjunctivitis or diarrhea. During the war Short noted among troops in North Africa 20 cases of dysentery and acute polyarthritis and 10 cases of polyarthritis, dysentery and urethritis or conjunctivitis or both. The condition was suggestive of Reiter's syndrome, but since stool cultures and agglutination tests incriminated the Shigella dysentery bacillus, the question arose as to whether Reiter's syndrome might represent latent Shiga dysentery. Others (Beiglböck) have commented on the ocular and urinary complications of "dysenteric arthritis" (Flexner) and Manson-Bahr,[115] commenting on Beiglböck's paper, concluded that "Reiter's disease appears to be nothing else than the familiar dysenteric polyarthritis with some superadded toxic manifestations which have been previously described." But dysenteric arthritis is not common and cases in which dysentery bacilli have been recovered from joints are rare. Perhaps Short's cases were not of dysenteric arthritis.

Cases of undoubted rheumatoid arthritis are complicated not infrequently by ocular lesions, occasionally by nonspecific urethritis or a brief diarrhea (see past Reviews [1]). Until we have more data and greater agreement as to the clinical definition, and in the absence of a diagnostic test or known cause, one should hesitate to make a diagnosis of "Reiter's syndrome." But such studies should be continued especially since certain strains of pleuropneumonia-like organisms are susceptible to streptomycin.—Ed.]

Pharmaceutic Arthritis and Arthralgia

Articular Reactions to Sulfonamides: "Sulfadiazine Arthritis." Most reactions to sulfonamides do not involve joints but three cases of febrile sulfonamide arthralgia were noted.

Fever, chills and polyarthritis developed in a case of chronic ulcerative colitis during each of four courses of sulfathiazole but not during later use of sulfaguanidine or succinyl sulfathiazole. The articular complication was from the drug, not from the colitis.[1922] Two cases of sulfadiazine arthritis occurred among 134 of meningococcic infections treated by Marangoni and D'Agati.[1153] One patient with meningitis had muscular and articular soreness without swelling. Various symptoms were relieved by sulfadiazine but after six days of therapy elbows and wrists suddenly became swollen, tender, painful and hot. Because of persisting arthritis and fever, doses of sulfadiazine were stopped on the thirteenth day. In 36 hours articular symptoms disappeared. "Arthritic pain" affected only three (0.6 per cent) of 500 patients given sulfadiazine; the pains promptly subsided on cessation of the drug.[1535]

Articular Reactions to Penicillin. Recently reported were one case of prompt, and several of delayed, sensitivity to penicillin with articular reactions like those of serum sickness. Present were moderate fever, painful polyarthritis, urticaria or pitting edema, sometimes erythema, adenopathy and dyspnea. Such reactions usually began seven to 14 days after penicillin therapy was instituted, sometimes five to nine days after its brief use was stopped, but in one case [911] twice within 48 hours after therapy was begun. Reactions lasted four or five days and were usually relieved by epinephrine alone or epinephrine in oil with the supplemental use of pentobarbital sodium or phenobarbital.[387, 406, 681, 735, 911, 1140, 1414]

Serum Sickness. Serum sickness involving temporomandibular joints resulting from tetanus antitoxin must be differentiated from onset of inadequately controlled tetanus. On a correct differentiation may depend the patient's life.

Turner and Clarke reported three cases of acute temporomandibular arthropathy (two after tetanus antitoxin, one after antipneumococcus serum). In one case a choice had to be made between risking death from tetanus (if the arthropathy represented impending "lockjaw" and if further antitoxin were withheld) or death from anaphylactic shock (if the arthropathy represented serum sickness and more antitoxin were given). The mechanism of serum sickness was studied by Karelitz, Glorig and Stempien.[951, 952] Patients convalescing from serum sickness after treatment with horse serum possess antibodies capable of passively sensitizing normal persons to horse serum.

Osteochondritis

Osteochondritis of Growth Centers. Varieties of this condition have, until recently, been regarded as separate disease entities and have acquired various eponymic designations (Osgood-Schlatter disease; Legg-Calvé-Perthes' disease). To emphasize their fundamental similarity some writers grouped them as "osteochondritis of growth centers."[1691] Almost every growth center in the body can be so involved. The osteochondritis probably results from any one of several causes.[651] Insufficiency of the blood supply to the involved epiphysis may play a causal rôle more important than trauma. Hypothyroidism was not a factor.[651]

Osteochondritis of the terminal phalangeal epiphysis of a finger of a child was noted (Staples[1691]). Reports on osteochondritis juvenilis of acetabulum are scarce: five cases (without involvement of adjacent femoral heads) were reported; in one the lumbar spine was also affected.[1113] Legg-Perthes' disease was discussed briefly.[639]

Traumatic Osteochondritis (Chondromalacia) of Patella. When a direct blow affects the patella its subchondral bone is compressed and areas of necrosis may develop therein and in femoral condyles. Repair may occur or the injured bone may be walled off and form a sequestrum. The following may then occur: gross interference with nutrition of overlying cartilage, degeneration of cartilage, irritation and hypertrophy of synovium with effusion, late progressive osteoarthritis (Cox).

Six cases were described.[399] Weeks or months after the acute posttraumatic symptoms subsided, mild chronic effusion appeared with vague pain in knees especially in the anterior compartment of the patella on kneeling or squatting. All patients noted occasional "locking" or "catching." Synovium was palpably thickened; synovial effusions and muscular atrophy varied in amounts. Crepitation or grating was elicited on passive motion of patella over femoral condyles. Pressure over patella or passive motion of patella caused pain. Roentgenograms were essentially negative although pathologic changes included: softening, fissuring and discoloration of cartilage of patellae and the anteromedial aspects of femoral condyles; thickening and villous degeneration of the synovium of suprapatellar pouch and anterior compartment of knee joint; pannus at edges of cartilage of patellae and femoral condyles; hypertrophy of infrapatellar fat pads.

The cartilage degeneration is not the primary lesion but is secondary to that in subchondral bone.[399] To relieve symptoms and prevent secondary osteoarthritis later in life patellectomy was preferred by Cox to patellaplasty (simple resection of affected cartilage): the six patients were completely relieved even though affected synovium, fat pads and femoral condyles were untreated.

[Patellar chondromalacia is the probable cause of many "squeaky knees."—Ed.]

To show the articular surface of patella and femoral trochlea a special roentgenographic technic (with the knee bent) was recommended.[1083]

Traumatic Osteochondritis of Professional Baseball Pitchers. Osteochondritis with loose bodies in the olecranon fossa often develops in elbows of baseball pitchers. Semidetached bodies also appear near the internal condyle and irritate the ulnar nerve. Surgical removal of loose bodies relieves symptoms and restores function (Bennett [123]).

Osteochondritis Dissecans. This refers to "an osteocartilaginous lesion of debatable etiology, characterized by a partial or complete demarcation of a segment of articular cartilage and subchondral bone, with or without ultimate detachment and extrusion into the joint." The literature was reviewed [1698] and 24 cases described: 20 in knees [286, 1063, 1698, 1736]; four in astragalus.[329, 347]

The condition results from posttraumatic necrosis of subchondral bone rather than from embolism or from osteochondral fractures, according to current writers.[347, 1698] Roentgenograms may be negative for as long as six months after the causal injury; in the absence of roentgenographic changes Langton [1063] considered diagnostic a typical history, tenderness over the point on the condyle likely to be affected, crepitus, a wasted quadriceps. Conservative treatment (rest, immobilization) was recommended for "slumbering," relatively symptomless cases [1698] and was successful in a child, aged four and one-half years.[1736] To prevent synovitis and later osteoarthritis, arthrotomy and removal of loose bodies was recommended [639]; excision of affected bone and cartilage was reserved for selected cases.[1698]

Tuberculous Osteochondritis of Ribs. Roentgenographic diagnosis of osteochondritis in the anterior ends of ribs can be made by making tangential exposures. Results in 12 cases of proved and 26 cases of probable osteochondritis of ribs were reported (Lindblom [1104]).

"Synovitis" and Synovial Cysts

No data appeared under "synovitis."

Synovial Cysts of Fingers. Called "synovial cysts," "synovial lesions of skin," "recurrent myxomatous cutaneous cysts," "periarticular fibromas of skin," these are fairly rare, but are occasionally associated with Heberden's nodes. Roentgenographic studies with diodrast showed a cyst connected with the joint. Eliassow and Frank concluded that "synovial lesions of the skin are due to an escape of synovial fluid from the joint cavity."

[Chemical and cytologic analyses were not made to determine whether the cystic fluid had the characteristics of synovial fluid. The small amounts of cystic fluid usually available would make such analysis difficult. One of us, W. B., found the fluid in such a synovial cyst to have a much greater content of calcium and to be much more viscous than normal synovial fluid.—Ed.]

Synovial Cysts of Popliteal Space; "Baker's Cysts." 1. Definition. Confusion as to the exact nature of Baker's cysts, popliteal or synovial cysts of the popliteal space was exhibited. In 1877 and 1885 Baker [62] described synovial cysts in the leg with disease of the knee; he stated that the cysts resulted from osteoarthritis. Later others reported a variety of popliteal enlargements as "Baker's cysts." [1039, 1235] Recent opinions were that Baker's cysts consist of (1) a posterior herniation of the capsule of knee (Kuhn and Hamphill [1039]);

(2) hernial protrusion of synovial membrane from the superior tibiofibular joint (Whalley); (3) semimembranous bursitis (Cottrell); (4) "enlarged semimembranosus bursa" (Burman [258]); (5) *either* posterior herniation of articular capsule (63 per cent of cases) *or* semimembranosus bursa enlarged by "hyperplasia-fluid distention" (37 per cent; Haggart [731, 732]); (6) generally "herniation of synovial membrane through posterior part of the capsule, or, less commonly, enlargement of either the semimembranosus or the medial gastrocnemius bursa by an escape of synovial fluid from the knee into either of these bursae via the normal anatomic connections between knee and bursae" (Meyerding and Van Demark). Because the term has been so misused or applied to so many different conditions, it was suggested that "the confusing patronym of Baker's cyst should be dropped" in favor of the more inclusive "popliteal cysts" (Burman [258]).

The popliteal cysts of children usually consist of enlarged semimembranosus bursae, those of adults usually comprise posterior herniations.[731, 732] Swelling from an enlarged semimembranosus bursa is more obvious on the medial side of the popliteal space; that from herniation is at or near the midline [731, 732]; other popliteal conditions to be differentiated were discussed.[1235] Neuritis with foot drop was caused in one case by compression of the external popliteal nerve by a Baker's cyst.[1917]

2. Pathology. According to Meyerding and Van Demark cysts were lined by endothelium but according to Haggart,[731, 732] sac linings, whether of herniations or bursal enlargements, were "mesothelial similar to the synovial membrane of the knee." That described by Whalley had a hyaline fibrous wall with no endothelial or epithelial lining. Even those who spoke of the bursal enlargements as "simple fluid-distentions" or "hyperplastic bursae" admitted that an acute or chronic inflammatory reaction of the serous and subserous layers of either bursae or synovial herniae often was present.[731, 732, 1235] Presumably the herniae or bursae contain synovial or synovial-like fluid but Ghormley and Dockerty [644] noted four "Baker's or popliteal cysts" which contained, not synovial fluid, but a solid mucinous (gelatinous or myxomatous) content; hence they were classified as "endothelial cysts."

3. Etiology. Trauma was considered the chief irritant by some [258, 731, 732] but not by Meyerding and Van Demark [1235] in seven of whose 15 cases rheumatoid or osteoarthritis of the affected knees was present. But if arthritis were a significant cause of "popliteal cysts," Burman [258] thought their coexistence would be more common.

4. Differentiation and Treatment. For accurate roentgenographic differentiation pneumograms were recommended by some,[1039] considered irritating or useless by others.[731, 732, 1235] Preferred treatment was surgical excision and closure of articular communications.[644, 731, 732, 1039, 1235] Small cysts producing mild symptoms may be treated by pressure pads.[1039] Use of sclerosing solutions was not approved.[1039]

Tumors of Synovia and Other Articular Tissues

Hemangioma. Only 29 cases had been reported through 1939.[16] In eight new cases [328, 764, 1863, 1990] two types were recognized: a diffuse form limited to synovial membrane, and a cavernous form with invasion of adjacent fascia and muscles. Features are characteristic: intermittent pain and swelling of a single joint usually since childhood; pain is usually mild; swelling and pain are augmented by standing, relieved by elevation of leg or compression of joint. Differentiation from hemophilic arthritis is important. Preferred treatment was

excision for the local (pedunculated) type, roentgen therapy for the cavernous type.

A "hemangioma of the elbow" in an infant 10 weeks old was successfully treated with radium.[945] The large ulcerating hemangioma was noted at birth over the left elbow "and forming part of the soft tissues of the elbow joint." [No roentgenographic or pathologic evidence was presented to show that the tumor was intra-articular.—Ed.]

Xanthoma. Xanthomas (giant cell tumors) affect tendon sheaths more often than synovial membranes or bursae; 25 new cases were reported.[407, 838, 1083] Jaffe, Lichtenstein and Sutro [906, 907] used the terms "pigmented villonodular synovitis, bursitis and tenosynovitis" to link tenosynovial xanthomas to the synovial and bursal lesions variously called "chronic hemorrhagic villous synovitis," "giant cell fibrohemangioma," "benign or malignant polymorphocellular tumor of synovial membrane."

Cystic Myxomatous Tumors. Reported were four cases of unusual mucinous tumors of knees including two which were probably cysts of menisci, examples of degeneration rather than true neoplasia (Ghormley and Dockerty). Endothelial linings were absent.

Synovioma (Synovial Sarcoma). 1. Clinical Data. Aitken [9] reserved the term "synovioma" for tumors derived primarily from cells of synovial lining and characterized by the formation within the tumors of spaces lined with synovial cells. It is a sarcoma, highly malignant or potentially so. Reviews of 76 [1071] and 104 [722] collected cases appeared. More than 50 new cases were described.[9, 109, 211, 462, 539, 562, 708, 722, 730, 788, 834, 889, 906, 1071, 1075, 1262, 1658, 1690] Included was the largest single series (16 cases) so far reported.[462] The term "synovium" has been stretched to include linings of tendons and bursae as well as of capsules; hence, some of the "synovial sarcomas" reported were of tendons or bursae.[906]

Of all previously reported cases knees were affected in 47 per cent [722, 1071]; lower extremities in 79 per cent of 104 cases; upper in 21 per cent. Symptoms were considered characteristic by some: [539] steady boring pain not relieved by rest or heat, progressive articular enlargement, flexion deformity of knee. But the chief features (pain, tumor, joint dysfunction, occasional effusions) were considered not characteristic by others.[462] Diagnoses are seldom made before surgical examination. Lewis [1h] described roentgenographic features pathognomonic of synovioma: scattered, irregular deposits of amorphous lime within a soft-tissue tumor-mass; these features were present in Aitken's case.[9] Most lesions are malignant.[788] Two benign lesions involving bursae were noted.[708, 834] Data on 45 collected cases of sarcoendothelioma were reviewed (Fisher [562]). A pathologic classification [462] and a method for culturing synovial sarcomas in vitro were described.[1283]

2. Treatment. In selected cases excision was considered feasible,[211] but recurrences and metastasis usually follow.[462] Since most synoviomas are resistant to radiation this was generally not recommended. No five-year cures have resulted from radiation alone, which does not even provide palliative relief.[708, 722] Amputation was considered: necessary only in selected cases,[9, 211] generally necessary,[1658, 1690] or the treatment of choice for all synovial sarcomas, although "delayed amputation" to allow for thorough histologic study of excised tissues is sometimes justified.[462] After reviewing results in 104 collected cases

Haagenson and Stout [722] recommended high amputation and possible dissection of regional nodes.

3. Prognosis and End Results. These were statistically discussed.[722, 1071] Five-year cures are uncommon. Metastasis generally affects lungs. One patient treated by excision alone (Haggart [730]) and one by "delayed amputation" [722] were well eight years after treatment.

4. Chondromatous Metaplasia of Synovia. One case was reported. Roentgenograms of knee showed "follicular calcification" in soft tissue. Diagnosis was impossible without biopsy. Multiple round foci of hyaline cartilage were developing in synovia.[1169]

5. Pseudotumors in Synovia. Two cases in knees were noted, one of "synovitis villosa hemorrhagica chronica" and one of benign synovial histiocytoma.[1246]

6. Synovial Osteochondromatosis. Removal of loose bodies is necessary to prevent secondary osteoarthritis.[639]

7. Malignant Lymphosis of Joints. No new data on leukemic infiltrations of articular tissues were reported.

8. Nonleukemic Myelosis. A patient entered the hospital seven times "because of 'rheumatism'": fever, pains in arms, legs and back. No articular swellings developed. A rare condition was present: chronic nonleukemic myelosis (Carpenter and Flory [292]).

Miscellaneous Types of Joint Disease

Clubbing and Hypertrophic Osteoarthropathy. Clubbing and hypertrophic osteoarthropathy, once considered independent phenomena, are related; the osseous changes of the latter represent a more advanced stage of the former process. An excellent review of their pathogenetic relationships was made by Mendlowitz. Various forms of clubbing and osteoarthropathy were described. Osteoarthropathy is much less common than simple clubbing.

Clubbing may be symmetrical, unilateral or unidigital. Symmetrical clubbing may be hereditary or acquired because of pulmonary, cardiac, gastrointestinal or other diseases. Clubbing may take years to develop or come on in a week. It may disappear if the primary disease is cured. Hypertrophic osteoarthropathy is an extension of the process of clubbing to more proximal parts of extremities and may develop in any condition capable of producing clubbing. Chief pathologic reactions are tissue hypertrophy and hyperplasia with the development of ossifying periostitis. But in the original bone, osteoclasis and resorption of bone may occur (Mendlowitz). Marked atrophy of terminal phalanges occurred in two cases of osteoarthropathy with clubbing (Weens and Brown).

Contrary to those who believe that clubbing is the initial phase, hypertrophic osteoarthropathy can occur without clubbing: a case was noted (Shapiro [1592]). Because of articular symptoms an erroneous diagnosis of rheumatoid arthritis is often made.[1173]

The fundamental cause is unknown but increased peripheral blood flow appears to be a chief factor.[1216] Hypertrophic osteoarthropathy was produced experimentally in a dog by anastomosis of pulmonary artery to left auricle causing an increased cardiac output.[1217] Present in current cases of hypertrophic osteoarthropathy were pulmonary neoplasms,[614, 1172, 1173, 1592] tetralogy of Fallot [1901] or postoperative myxedema and progressive exophthalmos (third such case recorded).[1523] In one case articular symptoms disappeared immediately after removal of a fibrosarcoma of lung.[1172]

Fried [614] reported four cases of pulmonary osteoarthropathy with bronchogenic cancer; clinical and necropsy findings led him to believe that the lung disease produced dyspituitarism which in turn produced the osteoarthropathy and that the latter condition "may not be remote" from acromegaly. A case previously diagnosed as hypofunction of pituitary secondary to acromegaly was considered by Bernard as one of multiple ossifying periostitis with hypothyroidism. A case of pulmonary osteoarthropathy in a dog with pulmonary tumor was noted.[1954]

Intrapelvic Protrusion of Acetabulum (Otto Pelvis). For intrapelvic protrusion of the acetabulum, Ghormley [639] recommended cup arthroplasty when possible, arthrodesis only when necessary. Acetabuloplasty was not successful.[639]

Congenital Anomalies. 1. Congenital Ankylosis of Elbow. This condition (congenital humeroradial synostosis) is a rare abnormality of which only 24 cases have been reported.[587, 616] Seven new cases were reported, one in a new-born babe (Murphy and Hanson [1276]). Of Frostad's five cases,[616] three occurred in one family, two in another. Four relatives of Frankel's patient [587] were similarly affected. Elbow spaces are still absent in the 22 mm. embryo; a dominant genetic anomaly results in continued complete absence of any elbow joint. In three of the four relatives of Frankel's patient [587] patellae were absent or rudimentary. Victims seem liable to fatal chronic nephritis.

2. Hereditary Triad: Arthrodysplasia of Elbows, Absence of Patellae, and Dystrophy of Nails. This results from an inherited congenital development defect of ectodermal and mesodermal layers of the embryo. Nails, especially of thumbs, are absent or thin. Patellae are absent or markedly hypoplastic. Elbows show prominent internal condyles, increased carrying angle, elongation and deformity with luxation of the proximal end of radius. Secondary osteoarthritic changes may occur. Thirty relatives of one patient were affected within four generations.[1582]

3. Aplasia of Interphalangeal Joints with Synostosis of Carpal and Tarsal Bones.[1621] Proximal phalangeal joints were rigid in the two cases noted, due to absence of joints from hypoplasia or aplasia. Other skeletal anomalies were present.

4. Hereditary Malformation of Hands and Feet. Fifteen members of one family within four generations presented a defect which was expressed variably from lobster claw and split foot to long thumbs or absent nails (Stiles and Pickard [1724]).

Tenosynovitis

General Comments. Reviews of the types of tenosynovitis, symptoms and current ideas on etiology and treatment appeared.[1112, 1442] Series of 190 [1112] and of 70 cases [1442] were analyzed. Types listed by Lipscomb [1112] included: (1) acute infectious forms due to pyogenic infections or gonorrhea; (2) acute noninfectious forms due to gout or trauma; (3) chronic specific infectious forms due to tuberculosis or syphilis; (4) chronic nonspecific infectious form in which no definite infectious agent is known but in which the pathologic reactions "resemble those seen in chronic infectious [rheumatoid] arthritis," and (5) chronic nonspecific forms, crepitating, noncrepitating or stenosing. Contrary to previous opinions no type of chronic tenosynovitis was considered to be "rheumatic" (Reed and Harcourt [1112, 1442]). Regardless of location, the presence or absence of crepitation or stenosis, Lipscomb [1112] considered trauma to be the usual cause and stated: "the various pathologic changes differ only in degree and depend primarily on the duration of the disease." Crepitation may or may not be present in any type of tenosynovitis and is by no means constantly present, even in so-called crepitating tendovaginitis.

Pathologic reactions in 16 cases were described: tendons were normal; tendon sheaths or peritendinous tissues (if sheaths were absent) were affected by serous effusions with clumps of fibrin, sometimes by proliferation of synovial linings with villous formation, occasionally by myxomatous degeneration or marked fibrosis with collections of hemosiderin.

Results of various treatments were analyzed. Currently favored was a program of "conservative treatment" of 20 [1442] or 60 days,[1112] with surgical exploration, if necessary, afterward (excision or incision of tendon sheath). Physical therapy alone gave poor results; roentgen therapy was slightly superior to surgical procedures.[1112]

Tenosynovitis, Tendinitis and Peritendinitis among Military Personnel. Traumatic tenosynovitis, although relatively mild, rendered large numbers of soldiers noneffective for duty. Of 63 cases among soldiers studied by Volk the Achilles tendon was affected in 42 (67 per cent), the extensor hallucis longus in nine, the tibialis anticus in five, other tendons in seven cases. Achilles tendinitis appeared "in almost epidemic form, early in the training period, usually after initial hikes." Some believe that neither the synovial membrane nor the tendon is involved, but peritendinitis is present, the tendinomuscular junction being affected.[1856] Relief resulted after a few days of hot foot soaks and rest.

Johnson [916] described a painful swelling over a tendon (usually Achilles, tibialis anticus or flexor tendon of the hallux) situated at a point of pressure such as a fold in the leather of a boot. If irritation continued, the localized swelling was transformed into a circumscribed elevated nodule closely adherent to the skin. However, it could be lifted off the tendon. Sometimes two nodules were present with a tender groove between. Biopsies showed avascular fibrous tissue with few inflammatory cells; tendon and sheaths were normal. Correction of boots gave relief.

Acute and chronic suprapatellar, sometimes infrapatellar, tenosynovitis and fasciitis affected certain pilots of heavy bombers whose leg muscles were in constant tense contraction for four to nine hours from pressing against the rudder during long flights. A stiff-legged, waddling gait and broad stance developed. Strapping the patella upward relaxed the affected tendon and gave immediate relief (Conway).

Tenosynovitis of Long Head of Biceps. This is usually caused by a sudden jar or pull. Pathognomonic are pain and tenderness along the bicipital groove. Much benefit and occasionally instant cure result from sudden traction on the arm and shoulder while the arm is relaxed and abducted; presumably the tendon is replaced in an improperly fitting groove.[1112]

"Snapping Thumb." This results from a lesion of the flexor pollicis longus tendon or sheath and is probably similar to stenosing tendovaginitis of the radial styloid.[1112] Two infants had stenosing tendovaginitis of a thumb. A striking feature was flexion deformity of the interphalangeal (distal) joint. Injury had occurred in one case, not in the other. Surgical splitting of the narrowed sheath, "the only treatment of value," was successful. Zadek [1988] stated that "trigger-finger" implies a "snapping" but this was not present in either of these infantile cases.

"Snapping (Trigger) Finger." This results from chronic occupational trauma. Like a "snapping thumb" it is caused by a stenosing tendovaginitis of a flexor tendon sheath at the metacarpophalangeal joint in the palm (Wood). Either narrowing of the sheath or enlargement of the tendon prevents free passage of the latter (Lipscomb [1112]). The reaction may be in tendon, not in the sheath; nodules may be found in the flexor pollicis longus tendon.[1112] Surgical correction was advised.

Crepitating Tenosynovitis (Peritendinitis). This may result from prolonged exertion of unaccustomed muscular effort. The primary lesion occurs in muscles ac-

cording to some, in tendons according to most. Roentgen therapy was preferred by some.[1112]

"Chronic Nonspecific Infectious Tenosynovitis." Marked cellular reaction (lymphocytes and plasma cells) "resembling that seen in arthritic tenosynovitis" was noted in one case.[1112]

Stenosing Tendovaginitis at Radial Styloid (De Quervain's Disease). About 250 cases of stenosing tendovaginitis at the styloid process of the radius have been reported.[1112] It affects chiefly women over 25 years old and occurred often in ex-office workers or ex-housewives who worked in war plants.[10, 1213] This type of stenosing tendovaginitis is identical with that which produces "trigger fingers" or "snapping thumb" (Meadoff and Gray). Clinical features, pathology and pathogenesis in 46 cases were reviewed.[10, 1112, 1213, 1344, 1405] Symptoms are produced by thickening of the fibrous sheath that covers the tendons and the synovial sheaths of the abductor pollicis longus and the extensor pollicis brevis as they pass through the bony groove in the radial styloid. A positive Finkelstein test is pathognomonic [10, 1405]: the thumb is placed in the palm of the hand and grasped by the remaining fingers. With the hand in this position even slight forced ulnar deviation at the wrist will produce excruciating pain. Surgical treatment is simple and "uniformly successful."

Tenosynovitis of "Baseball-Finger." The lesion of a "baseball-finger" may involve tenosynovitis as well as traumatic osteoarthritis. Rupture of tendon at the insertion of the extensor expansion into the distal phalanx of a digit may produce a "drop finger" with loss of extension at the distal joint (Wood).

Peritendinitis Calcarea (Calcareous Tendinitis). The exact locations of calcific deposits near joints has been disputed. The older view was that they were mostly in juxta-articular bursae, hence such terms as "calcific bursitis." On the basis of surgical dissections others (notably Codman, 1934) consider them practically always primarily within tendons and only secondarily, if at all, in bursae; hence, the term "calcific tendinitis." [948] According to Sandstrom whose work (1937–1938) is credited with bringing some order out of chaos, the deposits may be in tendons or tendon sheaths, in peritendinous tissue, ligaments or articular capsule; hence he considered the inclusive term "peritendinitis calcarea" more accurate. His view and term have been widely accepted,[373, 910] although some prefer such terms as "para-arthritis" [584] or "para-articular calcification." [1287] Thus many now consider calcific subdeltoid, trochanteric or radiohumeral "bursitis" to represent, not bursitis, but peritendinitis calcarea.[373, 947] Even Pellegrini-Stieda disease is regarded by some as a calcifying tendinitis.[19, 182, 246, 584, 1287]

Sites most commonly affected are shoulders, elbows, hips and knees; less often wrists, fingers, ankles, metatarsals. Of Frank's 14 cases [584] an elbow was affected in five, knee in four, hip in two, shoulder in one, hip and shoulder in one, wrist in one. Cases may be acute, chronic or latent (symptomless calcifications seen in roentgenograms). Acute or chronic microtrauma presumably damages the tendon with resultant decreased vascularity, necrosis of fibrous tissue, secondary calcification and in some cases even ossification.[373, 584, 910] The pathologic reaction was described [948] and illustrated.[373] To find certain deposits roentgenograms taken in special positions may be required.

1. *Shoulders.* These will be discussed under "Diseases about the Shoulder."

2. *Hips.* Calcific tendinitis may occur near the greater or smaller trochanter or close to the upper acetabular rim. Forty cases were discussed.[584, 948, 1992] Careful dif-

ferentiation from os acetabuli, sesamoids and capsular calcifications may be necessary; roentgenographic differentiation was nicely described by Zander.

3. Fingers. Calcareous tendinitis in fingers is "extremely rare." Ten cases were reported (Cooper; Zander [373]).

4. Wrist. The site commonly affected is "at the pisiform, probably in the tendon of the flexor carpi ulnaris." [373, 584]

5. Elbow. One case was reported.[584]

6. Knees. Some [182, 584, 947] who presented cases of "calcific tendinitis" or of "peritendinitis calcarea" at the mesial aspect considered this condition as equivalent to Pellegrini-Stieda disease. But according to others Pellegrini-Stieda disease is not a calcific tendinitis but is a calcific ligamentitis [19, 1287] or ossifying epiperiosteal hematoma.[1083] The relationships will be discussed under "Miscellaneous Conditions."

7. General Treatment. Of the various treatments discussed Frank [584] preferred rest and immobilization in acute cases, roentgen therapy in chronic cases. Roentgen therapy was favored by Zander [1992]: in a case with both hips affected the symptoms and calcific deposits disappeared rapidly from the radiated side and remained unchanged on the untreated side. Immobilization in plaster or splints for five to seven days, then physical therapy for one to three weeks cured Cooper's 78 patients.[373] According to Kaplan [947] rapid relief was afforded by procaine.

Diseases of Bursae

New anatomic studies were made.

Five bursae, hitherto undescribed, were located deep to the tibial collateral ligament (Brantigan and Voshell). Adventitious bursae are not present at birth but are acquired probably as a result of repeated trauma to soft tissue over a bony prominence. They develop as do normal bursae: connective tissue condenses and a fluid-containing cavity appears as a result of mucoid or myxomatous degeneration of connective tissue. Adventitious bursae, unlike true bursae, have no endothelial or other real lining. They are subject to the same diseases as true bursae: infection; enlargement; tumors; fibrosis.[242, 1045]

Etiologic Classification. A provisional etiologic classification was offered by Cherry and Ghormley. Among 41 bursae removed surgically, eight diseases were found. The only specific infection noted was tuberculosis. Tuberculosis usually affects larger bursae around large joints but tuberculous bursitis of a toe was noted.[812] Bursitis lateral to a greater trochanter is rare; when present it is often due to tuberculosis secondary to that of the trochanter (Donovan and Sosman).

Various Bursae: Clinical Data and Treatment. 1. Shoulder. Bursitis about shoulders will be discussed in the next section.

2. Elbow. An acute calcified bursitis near the lateral epicondyle of a humerus responded rapidly to roentgen therapy and diathermy. Absorption of calcium occurred (Young [1980]).

3. Groin. Cystic tumor of the iliopectineal bursa was seen in two cases, in one of which the tumor later connected with an arthritic hip (Stephens).

4. Hip. Tuberculous bursitis [477] was present in five cases; severe acute calcified trochanteric bursitis secondary to calcific tendinitis of the gluteus medius in seven.[1550]

In the latter cases fever, acute disability occurred for a few days only, then rapid recovery on rest in bed, applications of heat or cold, injections of procaine.

5. Knee. Ossification of an infrapatellar bursa and fat pad ("an osteoma") was relieved by surgical excision.[1475] In 10 cases "a new entity," noncalcific bursitis beneath the tibial collateral ligament, was treated successfully by procaine or excision (Voshell and Brantigan). Calcification of the most superior of the five newly discovered bursae deep to the tibial collateral ligament may account for *some* cases of Pellegrini-Stieda disease.[207]

The important bursae of the popliteal space may communicate with each other or with the joint. Communications with the joint are often open when the knee is extended, closed when the knee is flexed. The part these bursae play in the production of "Baker's cysts" is not agreed on (see "Synovial Cysts of Popliteal Space").

A case of traumatic degeneration of the medial head of the gastrocnemius simulating semimembranosus bursitis was recorded [348]: also one of osteochondromatosis of a popliteal bursa.[1989]

6. Heel. Inflammation of the posterior calcaneal bursa was common in the infantry. Retrocalcaneal bursitis was differentiated from Achilles tendinitis. Successful ambulatory treatment consisted of the application of cylinders of cotton behind malleoli, held in place by adhesive.[444]

7. Multiple Sites. A boy and two siblings presented large multiple calcified bursae in gluteal regions, an elbow, a foot. Studies on calcium balance were negative. Treatment was removal of bursae and the continued daily oral use of sodium citrate.[646]

General Treatment. Usually recommended were sulfonamides [312] [or penicillin—Ed.] for acute bacterial bursitis, drainage for acute suppurative bursitis,[312] excision for tuberculous or xanthomatous bursitis,[312, 477] single or repeated aspirations by some [312] or conservative nonsurgical treatment by the majority for acute traumatic bursitis. Roentgen therapy gave excellent results in cases of nonspecific, noninfectious bursitis, acute or chronic, calcific or noncalcific.[1401, 1980]

Hyperemia induces healing in acute or chronic nonspecific calcific bursitis: "anything causing increased vascularity causes absorption of the calcific deposit and cure." The inflammation which accompanies acute bursitis produces a curative hyperemia during which calcific deposits often resorb. According to Schein and Lehmann [1550] diathermy, static brush discharge, roentgen therapy, local applications of heat or cold, injections of procaine, aspiration of calcific material produce an increase in local hyperemia and the same general result with varying rapidity.

For chronic traumatic bursitis, so often not relieved by slow conservative methods, Burgess devised a "semiconservative procedure— simple paracentesis and internal bursotomy of the bursal sac creating a new communication between the sac and the adjacent subcutaneous tissue." Results were successful in 14 cases of chronic traumatic prepatellar or olecranon bursitis. It involved no time loss or disability for workmen.

Sclerosing solutions have not been widely used; too often they aggravate the bursitis without obliterating the sac.[255] An improved method was used by Cottrell: injections of sclerosing agents plus the use of a special type of rubber drain. Of 27 patients with chronic (olecranon, patellar or popliteal) bursitis with effusion so treated, 25 were rapidly cured. For chronic nonspecific bursitis not relieved by conservative means Cherry and Ghormley recommended surgical removal.

Diseases About the Shoulder Joint: The Painful Shoulder

Anatomy and Function. An improved knowledge of the normal function of the shoulder should lead to better diagnosis and treatment of its diseases. To this end the motions and functions of the shoulder of man and animals were studied by electromyograms (Inman, Saunders and Abbott) and by the fluoroscope (Fisk). Past writings have so stressed the motion of the scapulohumeral joint as to infer that movements of scapula, clavicle and sternum are of little importance. According to Fisk 50 per cent of the motion of the shoulder concerns the scapula and clavicle: "The scapulohumeral joint is responsible for only half the movement at the shoulder"; the range of motion at this joint is much more limited than is commonly supposed. The "shoulder joint" actually consists of four independent joints: the sternoclavicular, acromioclavicular, scapulothoracic and glenohumeral: shoulder motion is "the sum of movement contributed by synchronous participation of all these joint units."[895] Complete elevation of the arm depends on free motion of all these joints. "The old teaching that abduction to the right angle takes place entirely at the glenohumeral joint, and that thereafter, full elevation is completed by motion of scapula on the chest wall, is incorrect." On the contrary, motion occurs simultaneously in all joints of the region, each contributing its share. During early phases of elevation of arm, the sternoclavicular joint passes through its greatest range of motion; in the terminal phase, the acromioclavicular. "At the glenohumeral and scapulothoracic articulations, the ratio from almost the beginning to the termination of the arc, is respectively two to one, so that for every 15 degrees of elevation the glenohumeral contributes 10, the scapulothoracic 5 degrees." Ankylosis of any of the joints causes a permanent loss in degree of movement in direct proportion to the amount of movement that joint should have contributed.[895]

Terminology. More confusion appears to surround the subject of "painful shoulder" than any other topic in this Review. In current writings there is little harmony of thought among either physicians or orthopedists.

Terms used in 40 recent papers truly reflected "Babylonian confusion."[1775] In general, four main topics were discussed: calcific tendinitis or bursitis or both, noncalcific tendinitis or bursitis, tears of the musculotendinous cuff, and the "frozen shoulder" considered by some[1110, 1111, 1775] synonymous with "periarthritis." But these terms and the symptomatology diagnostic thereof were by no means clearly defined. Take, for example, the term "frozen shoulder." According to some writers this condition (a painful shoulder with motion limited in all directions and usually with no calcific deposits) is always, or almost always, caused by one lesion but there was no agreement on the lesion. It is (generally) caused by "adhesive capsulitis" (noncalcific synovitis and bursitis) according to one,[1297] by adhesive or obliterative subdeltoid bursitis according to others,[188, 310, 1206] by tenosynovitis of the long biceps tendon,[876, 1110, 1111] by acute calcific bursitis secondary to calcific tendinitis of one of the rotator muscles, generally the supraspinatus,[182] by "fibrositis"[1302] or idiopathic myalgia especially of the serratus posterior superior[1812] according to others. Others believed that several different pathologic lesions can produce the clinical picture identified as the "frozen shoulder."[182, 1207, 1775, 1935] They included: acute subdeltoid bursitis, "humeroscapular bursitis," chronic adhesive bursitis, calcific supraspinatus tendinitis, rupture of supraspinatus tendon, peritendinous and pericapsular adhesions ("adhesive capsulitis"), "interstitial fibrosis," bicipital tenosynovitis, "arthritis of shoulder joint."[182, 1206, 1207, 1297, 1775]

Some used the term "subdeltoid bursitis" with anatomic specificity; others as a general term under which they discussed a variety of lesions.[57, 182, 1205]

One writer stated [1205] that it is fashionable but incorrect to label most sore shoulders as "bursitis." To add to the confusion one writer used the term "supraspinatus syndrome" (in contrast to "supraspinatus tendinitis") to include a variety of lesions not of the supraspinatus tendon.[188]

Space does not permit analysis of what each writer meant by the terms used. Reading of a representative number of articles is suggested.[57, 182, 186, 188, 876, 921, 1110, 1111, 1206, 1207, 1322, 1775, 1935]

[Until terminology is less confused and the differential diagnosis of the lesions which produce "the painful shoulder" is better understood it would be well to adopt Bosworth's suggestion[188] that since a precise preoperative diagnosis often cannot be made, the clinical diagnosis should be given in two parts: (1) "internal derangement of the shoulder"; (2) the name of the lesion suspected but not certainly present as "internal derangement of shoulder: noncalcific supraspinatus tendinitis." We consider this a more "honest" and much less confusing method of nomenclature than that currently used, and as Bosworth stated,[188] the term "internal derangement" should be as applicable to the shoulder as to the knee. But some of the lesions under discussion are external to the shoulder joint.—Ed.]

Relative Incidence. As to the commonest cause of shoulder disability and the relative incidence of the various lesions disagreement was marked even among surgeons. Each of the following was voted the most common cause of shoulder pain: bursitis [1205]; rotator tendinitis [188]; arthritis of acromioclavicular joint [1322]; fibrositis of trapezius or adjacent muscle.[974] In 58 shoulders explored by Bosworth [188] tendinous lesions were found in 43; bursal in eight; osseous in five; none in two despite symptoms suggesting supraspinatus tendinitis.

Calcium Deposits About Shoulder. The roentgenographic incidence of calcium deposits about the 12,122 shoulders of 6,061 unselected persons "of the white collar class" undergoing periodic examinations was noted by Bosworth.[186] Calcium deposits were found in 165 (2.7 per cent) persons, in 202 shoulders. Males were affected more often than females; women typists more often than women clerks; right shoulders twice as often as left. Values for blood calcium were normal. The incidence of the deposits rose up to the age of 50 years. Many persons had bilateral deposits. Multiple deposits occurred in 20 per cent of affected shoulders: 51.5 per cent of involved shoulders had deposits in supraspinatus tendon, 44.5 in infraspinatus tendon, 23.3 in teres minor. Only five shoulders showed calcium in the subscapularis. Calcium was visible in the subacromial bursa in 25 shoulders.

The four short rotator tendons are the subscapularis anteriorly, the supraspinatus and infraspinatus above, and the teres minor posteriorly.[190] But as these tendons become indistinguishably fused to form the capsule of the shoulder joint (conjoined tendon or musculotendinous cuff), it is difficult to determine which tendon contains the deposit. Bosworth [190] located them by fluoroscopy and by noting "the rotation of the arm which brings the deposit in profile." But Baird [57] considered it impossible in most cases to determine the exact anatomic location of these deposits roentgenographically. According to Howorth [876] supraspinatus calcifications are located just above the junction of the greater tuberosity and head of humerus; those of infraspinatus and teres minor are lower and superimposed on the tuberosity except in

internal rotation; those of subscapularis are superimposed on the joint in internal rotation, on the head in external rotation. Of Howorth's 100 patients [876] 40 per cent were men, 60 per cent women; most of these deposits affected the supraspinatus, "several" the infraspinatus or teres minor, only one the subscapularis.

In explored shoulders the deposits were rarely located in the bursa alone; almost always in the supraspinatus tendon which forms the floor of the subdeltoid bursa.[876, 923, 1205] The general opinion was that the deposits are primarily in the tendon and may rupture into the overlying subdeltoid bursa. Many small deposits disappear without symptoms; cases of silent or quiescent calcific tendinitis are numerous. But in Bosworth's [190] experience "large deposits always result in a painful shoulder sooner or later, though they may remain quiescent or symptomless for months or years." Of 202 affected shoulders which Bosworth [190] followed for three years 132 (65 per cent) were painless, 70 (35 per cent) became painful, 18 acutely, 52 "mildly" or "slightly."

The exact relationship between calcium deposits and acute attacks was disputed. In general the size, number or location of deposits was not proportional to symptoms and signs of disability.[57, 876] According to most writers, the degenerative changes and calcium deposits in avascular tendons are symptomless; only when calcium ruptures into vascular peritendinous tissue does inflammation occur; when it ruptures from the supraspinatus tendon into the overlying subdeltoid bursa, acute chemical bursitis occurs. [57, 182, 190, 1206, 1935] However, according to Howorth [876] acute attacks are not due to rupture of tendinous calcific deposits into bursae but to the increased tension produced in the tendon; when the deposit ruptures into bursa "immediate relief" occurs.

Lesions of Individual Tendons. Any of the five tendons of the shoulder (the four rotators and the long head of the biceps tendon) may be affected by (1) degenerative tendinitis without calcification, (2) calcific tendinitis, or (3) partial or complete rupture. The supraspinatus was most often affected.

The causes of tendinitis (acute or chronic, calcific or noncalcific) are not precisely known. No relation to focal or systemic infection has been proved; cultures of affected tendons and adjacent bursae have been negative.[186, 465, 876, 1935] The tendinitis bears no relation to arthritis or rheumatic diseases.[186] Deficiencies of vitamin C [1935] or E [1749] or an endocrine disturbance have been suggested but not proved.[465, 1515] Repeated exogenous trauma is not a proved cause [57, 190] and according to some [190] single acute direct trauma practically never damages rotator tendons. Endogenous trauma was generally regarded as the main cause of the tendinitis: occupational trauma related to abduction and twisting [57, 190, 465] produces attrition and "use-destruction." [310] Microscopic tears lead to degeneration and necrosis.[57, 876, 1206] If tendons are affected by fatty degeneration, saponification and precipitation of calcium carbonate result in "calcific tendinitis." But if hyaline degeneration occurs, no saponification or calcium deposition results and the reaction in tendon (or associated bursa) is serous: serous exudate; precipitation of fibrin; formation of loose adhesions caused by fibrin rather than fixed adhesions from fibrous tissue.[182] Quiescent calcific tendon lesions are supposedly "those in which the deposit is buried deeply enough in tendon tissue so that no peritendinous (bursal floor) irritation takes place." [1206]

Bicipital (noncalcific) tenosynovitis is the commonest cause of "frozen shoulder" according to Lippmann [1110, 1111]; it was present in 26 of 30 cases. The symptoms, pathology and pathogenesis of bicipital tenosynovitis were reviewed. "Spontaneous cure inevitably results" when the tendon fuses to the bicipital groove after three months to two and one-half years. Conservative treatment is justified unless a rapid cure is desired; the latter is accomplished by suturing the tendon to the lesser tuberosity. Despite the appearance of a "frozen shoulder" no true contracture of articular capsule is present as surgical release of the tendon immediately restores full motion of shoulder.

Supraspinatus tendons may be affected by calcification and ossification or laceration.[188]

Among unselected cadavers studied by Jones [921] lesions of supraspinatus tendon were present in 30 to 40 per cent; large complete ruptures in 15 to 20 per cent. In a study of cadavers Wilson and Duff found complete rupture of supraspinatus tendon in 22 per cent, partial rupture in 20 per cent, rupture of bicipital tendon always secondary to that of the supraspinatus in 7 per cent. A normal supraspinatus tendon does not rupture; degeneration must occur before traumatic rupture occurs (Wilson [1935]). Calcific deposits are rarely present in ruptured tendons (Baird [57]). Symptoms, signs and roentgenographic features of ruptured tendons were discussed; treatment involves operative repair.[57, 188, 876, 1935, 1936]

Lesions of Conjoined Tendon. Lesions of the musculotendinous cuff produce symptoms much like those of other lesions just described. The nature, location, symptoms of complete and incomplete tears and treatment were discussed.[190, 1205, 1297] Neviaser regarded adhesive capsulitis as the chief cause of frozen shoulder and recommended manipulation under anesthesia.

Lesions of Bursae. It is accepted that the subdeltoid and subacromial bursae are "one and the same": when the arm is abducted the entire bursa is subacromial; when it is adducted much of the bursa is subdeltoid.[923] According to most writers subdeltoid bursitis, calcific or noncalcific, is never a primary entity but always secondary to some lesion near by, generally in the supraspinatus tendon (tendinitis, tear or calcific deposit) which forms its floor.[713, 1935] McLaughlin [1205] went a step further and stated that when subdeltoid bursitis is present "it usually constitutes a second condition having no connection with the primary lesion other than proximity." Subdeltoid bursitis is the "inevitable result" of calcific tendinitis, according to Bosworth.[190] Most writers supported Codman's (1934) view that calcific deposits are practically never in the bursa but in the tendon beneath [923, 1205]: Howorth [876] found calcium in only one of 23 bursae explored but Baird noted one bursa "completely filled" with calcium. Pathologic reactions in bursae were described.[465, 876] The bursitis may be serous (noncalcific) or calcific [982]; acute, subacute, chronic or quiescent. Laceration of bursal floor without involvement of tendon occasionally occurs.[188] "Subacromial bursitis" may be secondary to, or associated with a disorder of the central nervous system, according to Dynes.

Treatment of Tendinitis and Bursitis. 1. General Comments. Physicians wrote mostly about the treatment of calcific tendinitis and bursitis, less about ruptures and little about other noncalcific lesions. Distinctions between the treatment of calcific and noncalcific inflammations were poorly made: remedies for both were about the same except that for calcific lesions physicians, especially orthopedists, revealed an almost unconquerable urge to remove the calcium. Tears of tendons or cuffs were usually treated by surgical repair.

The following pertains to calcific tendinitis and bursitis. Calcium deposition in tendons is a reversible process; unless they are large the deposits are generally absorbed by any process involving acute hyperemia. The mechanics of precipitation and resorption of calcium were discussed.[1935] Even an acute inflammatory reaction itself carries with it the mechanism for calcium absorption. This is why so many deposits disappear rather rapidly after almost any treatment for the acute attack or even with none. Therefore conservative measures were recommended in most acute cases. Surgical measures were reserved for chronic conditions unrelieved by conservative measures or for acute cases in which resolution and healing appear tardily or "a rapid cure" is desired. No remedy was successful in all cases: 50 per cent of patients were readily relieved by this or that remedy. Results of almost any measure were good in acute cases, often disappointing in chronic cases.[57, 186]

2. Conservative Measures. Physical therapy was considered of real value by some,[124, 500] of use only as an adjuvant,[186 465, 876] or usually unsatisfactory.[310] Calcium deposits are only affected by long wave diathermy according to Echtman.[500] Solomon and Morton [1673] regarded diathermy as useful as roentgen therapy. Sometimes cold was preferred to hot applications which may occasionally aggravate symptoms.[876] Prolonged physical therapy may be more expensive and less suitable than other measures including surgery.[186] Immobilization by splints and plaster during acute attacks was condemned: it fosters formation of adhesions and stiffness.[186, 876, 1935] Manipulation under anesthesia may be "disastrous" (Howorth [876]). Ammonium chloride given orally to hasten absorption of calcium gave results in five cases of calcific supraspinatus tendinitis satisfactory to Dick, Hunt and Ferry.[465] Results of intravenous injections of iron cacodylate given by Pelner [1362] were negative in calcific bursitis, presumably "spectacular" in noncalcific subdeltoid bursitis. Synthetic vitamin E (alpha tocopherol) was valueless [1749]; neostigmine useful.[938, 1815]

Roentgen therapy was the most favored conservative measure and was considered by most writers to be satisfactory in cases of acute or chronic calcific or noncalcific tendinitis or bursitis.[57, 310, 774, 923, 1401, 1980] Sometimes symptoms rapidly subsided and calcium deposits disappeared.[57, 182, 923, 1515] Results were best in acute cases or in chronic cases in which the deposits were soft, fuzzy and small, less notable in chronic cases or in acute cases with large, dense, discrete deposits.[182, 876] Roentgen therapy dilates capillaries, increases their permeability, leads to phagocytosis of fibrin and necrotic tissue. The effect is not a direct one on the deposits; it does not affect quiescent calcific deposits (Borak [182]).

3. Surgical Measures. Each of the following remedies received enthusiastic support and apparently gave excellent results especially in acute cases. Injections of procaine relieved acute subacromial bursitis without calcification.[713] Simple needling and infiltration of calcific tendons or bursae with saline promptly cured other acute cases.[947, 1065] Multiple needling, or needling and aspiration of calcific material was used successfully by some [1206] but not by others.[876, 947] Irrigation of acutely inflamed bursae by means of two needles for inflow and outflow was approved by some [982, 1345] but considered difficult, unsatisfactory and less helpful than surgical excision by others.[190, 876, 1935] Block anesthesia and manipulation were used by Tarsy.[1775]

For acute calcific tendinitis or the "acute supraspinatus syndrome" operative drainage, incision of tendons and excision of necrotic calcific material were considered best by several workers [186, 713, 876, 1206, 1935]: Average hospital stay is only four days and "immediate, certain, complete and permanent relief" results (Bosworth [186]). "There are only two forms of therapy simulating nature's method of cure (extrusion of calcium from tendon) and having proved curative effects, opening of the deposit by knife or needle" (McLaughlin [1206]).

For acute posttraumatic noncalcific lesions of shoulder unrelieved by one or two weeks of conservative therapy or for intractable chronic cases surgical exploration was recommended: in such cases unsuspected tears and other lesions amenable to surgical repair are often found.[921, 1206]

Lesions of Joints. Rheumatoid or osteoarthritis of acromioclavicular joint was regarded by Oppenheimer [1320, 1322] as a more common cause of painful shoulder than heretofore suspected. For it he recommended roentgen therapy. In the "frozen

shoulder" the synovia and cartilage of the joint are not affected.[182] But no articular lesion was found responsible for any of Bosworth's 53 cases of painful shoulder. A case of posttraumatic pericapsular ossification and ankylosis was noted.[707]

Lesions of Muscles. Fibrositis of trapezius or adjacent muscles, or "idiopathic myalgia" of muscles of back and shoulder, especially of the serratus posterior superior muscle were considered common causes of "painful shoulders." [1302, 1812] Procaine infiltration of tender spots was recommended.

Lesions of Bone. Irregular destruction and cystic lesions of the humeral head may be associated with severe or chronic tendinous lesions. Among Bosworth's cases [188] of "supraspinatus syndrome" were two of humeral osteochondritis.

"The Shoulder-Hand Syndrome." As a complication of about 10 or 20 per cent of cases of coronary occlusion, less often angina pectoris, shoulders may be affected by pain alone or by painful stiffness (Howard, 1930; Eideken and Wolferth, 1936; Ernstene and Kinell, 1940). Sometimes a hand is affected; "the shoulder-hand syndrome." [1302]

In Askey's 22 cases of the latter, pain and stiffness affected generally a shoulder one week to seven months after coronary occlusion or angina; a few weeks later a hand was affected becoming painful, stiff and swollen with tense glossy discolored skin and markedly limited motion simulating sclerodactylia. The whole hand was affected, not just joints. Palmar thickening resembling Dupuytren's contracture sometimes developed. Pain in shoulder or hand was severe, at times requiring narcotics. Pain affected a right shoulder and hand in 11 cases, left shoulder and hand in 10, both sides once. A consistent point of maximal tenderness corresponded to the site of trapezius branches of cervical plexus. Curiously pressure over this spot sometimes relieved pain temporarily, once permanently. The disability lasted several months to two years (average six months). Residual stiffness usually resulted.

Six to eight weeks after myocardial infarction hands and wrists were affected by "periarthritis" in three cases of Meyer and Binswanger. Shoulders or hands or both were affected in 39 of 178 consecutive cases of myocardial infarction studied by Johnson [914] who termed the condition "post-infarction sclerodactylia." In these 39 cases "joints" became affected three to 16 weeks after the infarction. Pain, limited motion, atrophy and palmar contractures affected the hands. Johnson [914] considered the "periarthritis" of shoulders to be unrelated to the disability of hands. At necropsy an affected shoulder in one case was entirely normal. Six cases of Dupuytren's contracture (four of painful stiff shoulders) after myocardial infarction were noted by Kehl.

Thirteen cases of painful shoulder with effort angina or myocardial infarction were noted by Travell, Rinzler and Herman.[1812] A "frozen shoulder" may also complicate pulmonary disease (Lippman [1110]). [No data given.—Ed.] The relation of myalgia and arthralgia of the left shoulder to coronary disease was also discussed by Harrison. After hemiplegia or Parkinson's disease "subacromial bursitis" may develop, so stated Dynes. [In these cases the "bursitis" may have represented an incomplete "shoulder-hand syndrome."—Ed.]

Askey regarded the condition as "a combination of sympathetic nerve disturbance and arthritis." According to Johnson [914] the involvement of hand may result from "anoxia of the tissues of fingers produced chiefly by ischemia resulting from reflex vasoconstriction of arteries of hand induced by cardiac pain." An "irritation of sympathetics" was blamed by Kehl.

Various treatments given by Askey were valueless including salicylates and paravertebral injections of alcohol into first and second dorsal sympathetic ganglia.

[The "shoulder-hand syndrome" also may occur after hemiplegia, splinting of an arm after fracture, manipulation of a shoulder or "spontaneously." This phenomenon possibly may be related to the painful vasomotor disturbance, causalgia or Sudeck's bone atrophy even though the former is presumably related to ischemia and the latter to vasodilation.[463, 464]—Ed.]

Miscellaneous Causes of Shoulder Pain. Various other causes of painful shoulders were noted: acute epidemic myalgia of neck and shoulders [111, 112]; lesions of cervical spine—osteoarthritis, tuberculosis, malignancy, herniated disks [355, 749, 1237]; scalenus anticus syndrome,[935] cervical rib,[422] and other neurologic lesions.[1683, 1975]

Diseases of Muscles and Fibrous Tissue

Diseases Caused by Trauma. 1. Traumatic Myositis. The mechanism of injury, diagnostic features, pathology and treatment of muscular injuries, particularly in athletes, were reported (Northway). Under the term "traumatic myalgia" Good [674] discussed what others would have called "fibrositis related to trauma."

2. Traumatic Myositis Ossificans. This type of myositis ossificans is more common in the brachialis muscle than elsewhere in the body; it is usually a late complication of posterior dislocation of the elbow (Loomis [1125]). The relation of traumatic myositis ossificans to injuries of nerves was discussed: such cases, sometimes mistaken for bone sarcoma have led to "surgical disasters" as amputations (Brailsford [204]).

Myositis Ossificans Progressiva. Cases of the progressive, nontraumatic form of myositis ossificans were noted.[1335, 1520, 1853] In 75 per cent of such cases a congenital anomaly is associated; an unusual case without such anomaly was reported (Ryan [1520]). In one case the condition developed subsequent to disseminated congenital osteomas of skin [1853]; in another it was associated with sarcoma in muscles overlying a scapula.[1335] In two cases osteogenic sarcoma developed in a pre-existing myositis ossificans circumscripta (Pack and Braund [1335]).

Suppurative Myositis. Gonococci were recovered from a swollen left calf in a case of suppurative gonococcic myositis and arthritis.[1107] A case of suppurative anaerobic streptococcic myositis [799] and one of staphylococcic myositis [1844] were noted.

Tropical Myositis. This is an acute purulent or nonpurulent myositis common in the Eastern tropics: it is presumably identical with primary suppurative myositis as seen rarely in the United States. Neither the infecting germ nor the mode of its entry is constant. One or more microorganisms may be recovered, most often staphylococci, streptococci, colon bacilli or combinations of these. A case due to hemolytic streptococci was reported from North Carolina (Cockrell).

Myositis from Scurvy. In an outbreak of scurvy among prisoners in Kenya painful tender indurated swellings affected various muscles especially of the

calf; they resembled somewhat nonsuppurative tropical myositis (Wiseman[1953]). Under therapy with vitamin C (lemons) symptoms disappeared and no new cases occurred.

Trichinosis: "Trichinal Rheumatism." The examination of 5,313 diaphragms from 189 hospitals in 37 states revealed an average incidence of diaphragmatic lesions of 16 per cent, exposure to trichinosis being nearly uniform regardless of geographical or environmental factors (Wright and Walton).

The clinical similarity between trichinosis and periarteritis nodosa may be so great that differentiation is impossible without microscopic evidence. In two cases regarded by Reimann, Price and Herbut as trichinosis, typical lesions of periarteritis nodosa were found in tissues during life. Present were symptoms of "trichinal rheumatism": painful shoulder and masseter muscles; recurrent arthritis; fever; periorbital edema; conjunctivitis; eosinophilia. In one case precipitin tests with Trichinella antigen were positive in high dilution but trichinellae were not found in muscles. In the other case painful muscles, acute arthritis of knees and ankles, and intramuscular encysted larvae were noted; biopsies revealed evidence of periarteritis nodosa before, but not after, death. "There is a possibility that trichinosis as a disease with strong allergic manifestations may in certain instances serve as one cause of the syndrome called periarteritis nodosa."

Epidemic Myositis or Myalgia. 1. Epidemic Pleurodynia; Bornholm Disease. Clinical features of Bornholm disease are high fever, prostration, pleural and abdominal pains; involvement of trapezius muscle is rare as are also widespread muscular symptoms. In recent epidemics there were unusual features. Among 166 cases in Brooklyn (1942), a high incidence of pharyngitis and meningoencephalitis was noted. Most of the affected children had convulsions [873]; 11 of 16 nurses had involvement of central nervous system.[1188] Muscles around shoulder and neck were notably affected in Ronald's 12 cases, presumably from referred pain resulting from involvement of diaphragm or diaphragmatic pleura. Clinical and epidemiologic aspects in 75 cases occurring near Mobile were reported.[1300] Outbreaks affected military personnel.[12, 1192]

2. Other Forms of Epidemic Myositis. A "hitherto undescribed form of epidemic myositis" was seen by Williams [1926] in five young recruits after inoculation with tetanus toxoid and T.A.B. vaccine. Myositis affecting abdomen, chest, shoulder, pelvic girdle and limbs developed with meningeal symptoms, neuritis and erythema.

[Could this not have been atypical epidemic pleurodynia with meningeal symptoms as noted in the preceding paragraph, the condition being only coincidentally related to the immunization therapy?—Ed.]

At present Bornholm disease is the only recognized form of epidemic myalgia. The common "stiff neck" or acute torticollis may represent another form of epidemic myalgia. An epidemic of "stiff neck" occurred in England in 1941: 125 cases were studied by Beeson and Scott.[111, 112] Trapezius muscles were chiefly affected, sometimes deltoids and sternomastoid. Abdominal and pleural pains were absent. Symptoms resembled the common sporadic "stiff neck" of acute fibrositis. Most cases were mild and of short duration but occasionally the disease became chronic, involved other muscles and resembled generalized

fibrositis—cases which "would not ordinarily be identified as having originated from an epidemic of benign myalgia of the neck." Transmission to human beings appeared to be accomplished through the agency of whole blood from acute cases. Perhaps cases of so-called sporadic acute fibrositis of neck sometimes represents an undetected epidemic.

A small epidemic of acute myalgia affected members of a nursing staff: one to three weeks after an acute sore throat seven nurses developed fever, pains in muscles of chest and extremities which persisted somtimes for five months. A myotropic virus was held responsible (Houghton and Jones).

During an epidemic of atypical poliomyelitis studied by Rosenow cases were seen which culminated "in a strange and painful disease or state" called "encephalomeningoradiculitis with fibromyositis"; streptococci in water supply were the suspected cause.

"Myalgia"; "Myalgic Spots." The main objection to the concept of fibrositis is our lack of knowledge of its pathology (Collins [358]; Gordon [682]). It has been difficult to demonstrate it or to confirm the meager data of early workers (Buckley [243]; Stockman [1730]). In the United States and to a lesser extent in Great Britain, "the home of fibrositis," many physicians have hesitated to make a diagnosis of fibrositis or have used the term reluctantly and with dissatisfaction. Stimulated perhaps by the work of Kellgren (1938) [1f] many writers are now discussing under the noncommittal term "myalgia" what they formerly would have called fibrositis. Instead of "fibrositic nodules" we now read of "myalgic spots," [377, 979, 1950] "tender spots," [423, 519] "trigger zones" [1623] or "trigger points." [1829] These myalgic spots are to be zealously sought and injected with procaine with the expected relief of referred pain in many near-by or distant regions. Some attempted to differentiate "myalgia" from "fibrositis." Thus Williams and Elkins [1928, 1929] discussed "myalgia of the head" and "myalgia of the pharynx" (severe sore throat, painful swallowing, occasional hoarseness but negative examination) as functional disorders in muscles sensitized to some chemical agent, perhaps histamine.[1927, 1928, 1929] Others [673, 1950] seemed to use myalgia and fibrositis interchangeably. Because the distinctions, if any, are not clear we will discuss both topics under the next section on "Fibrositis."

Fibrositis

This is the most common form of acute and chronic rheumatism (Slocumb [1624, 1627]), but the term is "too loosely applied and ill-defined" (Ellman and associates [524]). Because of its variable manifestations "it marches under false banners, assumes numerous disguises, and is known by a variety of aliases" (Swett [1760]).

Incidence. Fibrositis affected 52 per cent of rheumatic out-patients and 20 per cent of rheumatic in-patients at a British army hospital in one year (Savage [1541]). In another British army series of rheumatic patients 69 per cent had fibrositis (Hutchison). Among rheumatic American soldiers the relative incidence of fibrositis was only 4.7 per cent of 214 consecutive cases at one army hospital (Boland and Corr). The incidence of nodules was noted by Copeman and Pugh: among 500 soldiers nontender nodules were found with equal frequency in fibrositic and nonfibrositic subjects, but tender nodules were 10 times more common in those with true fibrositis. In 31 per cent of 100 cases of chronic sciatica in young people fibrositis was the supposed cause

(Jackson). The highest incidence of "rheumatism" occurs in miners; fibrositis affected 42 per cent of 113 rheumatic British miners (Schmidt[1553]). It is uncommon in youth, reaching its peak incidence in the fifth decade of life (Steinberg[1703]).

Etiology. Two forms of fibrositis, (1) primary fibrositis, (2) a secondary form, from trauma, infection or arthritis, were again described.[1037, 1624, 1627, 1703] Trauma was considered a common factor,[674, 1267, 1541] either as a single event or from repeated strain, such as produces lumbago in gardeners or Dupuytren's contractures in racing drivers or surgeons.[1760] Foci of infection were considered a minor factor.[358, 524, 890, 1541] A relation to exposure seemed more definite: half of 50 fibrositic patients were in occupations favorable to the development of rheumatism.[524] In miners cold and damp are primarily responsible.[1553] Copeman[377, 378] suggested that such factors as chills, damp, trauma may be of secondary importance and will provoke an attack only in the presence of latent "myalgic spots" previously formed during an illness such as influenza. A relationship to influenza was reported in eight of Jackson's cases.

Often the onset or recurrence of "fibrositis" is precipitated by emotional upsets and is alleviated when the life situation improves, according to Halliday.[747] This view was challenged by Kelly[978, 979]: "the symptoms can be explained on the basis of known somatic reactions rather than of mystic symbolism or emotional delusion." Others discussed the psychogenic factor.[524, 682, 890, 1627] Unilateral fibrositis of shoulder muscles in a group of London women was prosaically called "queue-itis" and was presumably due to long holding of market bags (Cutner). Other causal factors mentioned were metabolic and endocrine disturbances,[524] postural defects,[476] coronary heart disease,[780, 1829] circulatory insufficiency,[1760] plumbism and alcoholism.[1703] Steinberg[1703] considered primary fibrositis a metabolic disorder related to vitamin E deficiency.

Clinical Data. Fibrositis was defined as an acute, subacute or chronic condition affecting subcutaneous tissues, fibrous origins, insertions and aponeuroses of muscles, fibrous portions of joint capsules, fascial ligaments or tendons and supporting tissues of certain nerves (Collins[358]). Physical examination may be negative.[524] Many authors recalled the idea of Kellgren (1938)[1f] that the muscular pain may be referred, the site of local tenderness being quite apart from the site of the pain. Common sites for fibrositic lesions were described.[673, 677, 890, 978, 1037, 1631, 1703, 1825, 1950] Fibrositis is a common cause of low back pain,[862, 973, 1541] sciatica,[245, 760, 862, 904, 972, 1541, 1730] or postoccipital pain and headache.[972, 975, 1267, 1376, 1541, 1730, 1928] It must be considered in the differential diagnosis of shoulder pain.[111, 978, 1541, 1829] Fibrositic lesions of chest wall and around knee and foot were described.[972, 977, 979, 1631]

[Feet are rarely, if ever, affected by *primary* fibrositis.—Ed.]

The rôle of fibrositis of abdominal, dorsolumbar or psoas muscles in the production of abdominal pain which may easily be confused with visceral lesions was stressed by many.[720, 760, 789, 862, 973, 1267, 1622, 1760, 1825] In 50 cases low abdominal pain was attributed to psoas fibrositis (Greene). Fibrositis may produce thoracic pain[973, 1760] which sometimes resembles angina.[245, 862, 1267] The "dorsolumbar syndrome" was vaguely defined as a localized fibrositis of the back with pain referred along the twelfth thoracic and first lumbar nerve producing symptoms in back, abdomen, groin or scrotum.[1622] Fibrositis of orbital muscles was reportedly encountered.[471]

In diagnosis, Mester's "specific reaction" was not found of value (Copeman and Stewart). Diagnostic movements to localize deep-seated lesions were outlined (Cyriax [420]).

[Obviously old confusions still prevail. Since the manifestations of primary fibrositis are largely, if not entirely, subjective, many "aches and pains" of diverse nature and cause are erroneously labeled "fibrositic." Studies on the relative frequency of rheumatic diseases among British troops indicate an incidence of "fibrositis" many times that among American troops subject to the same etiologic factors, and that no cases of "psychogenic rheumatism" were listed as such. We suspect that many of these cases of "fibrositis" among British soldiers and civilians [524] really were of "psychogenic rheumatism."

We are skeptical about "abdominal fibrositis." In our experience many vague abdominal pains, the cause of which physicians cannot determine, are "disposed of" as "fibrositis of abdominal muscles." If this is so, why do not the "fibrositic abdominal muscles" react to rest, changes in weather, sleep, exercise, heat, cold, as do fibrositic muscles elsewhere? The whole subject of primary fibrositis needs more critical appraisal and much more study. It is regrettable that we know so little about disease of skeletal muscle which comprises 40 per cent of the weight of the human body and is even more available for biopsy than articular tissues.—Ed.]

Pathology and Laboratory Data. Older ideas on pathology were reviewed.[243, 358, 682, 1730] But recent studies did not reveal any characteristic tissue change.[358, 608] Steinberg [1703] considered the pathologic changes of primary fibrositis similar to those of nutritional muscular dystrophy.

Creatinuria was found in 19 of 20 patients with myosis (myalgia), the output being somewhat proportional to symptoms.[215] Electromyographic examination of fibrositic patients has shown increased localized irritability of muscle in some cases (Elliott [518, 519]), but no abnormality in most (Brøckner-Mortensen and Clemmesen [215]; Buchthal and Clemmesen). No change in liver function or plasma volume was found (Robinson [1480]). Blood studies were of little help; sedimentation rates were usually normal,[727, 1624, 1627] but may be elevated (Race; Swett [1760]). An elevation of blood uric acid in some cases suggested a gouty basis (Buckley [243]; Race). The plasma fibrinogen level was increased in "chronic muscular rheumatism" (Mester [1224]). The urinary excretion of vitamin C was usually decreased, that of indole increased (Race).

Treatment. The value of rest, heat, massage, salicylates and correction of postural defects were again noted. Rest is essential in acute cases.[476, 890, 1760] Skilled, heavy massage [471, 789, 1037] and "stretching" exercises [1037] were recommended. Such measures are effective even in "the fibrositis of old age." [874] Most writers reported successful results from the injection of local anesthetics into "trigger points," [424, 673, 677, 972, 975, 977, 1541, 1622, 1829] but Hutchison [890] stated that his early enthusiasm for such injections had been tempered by further experience. Failures resulted when all tender areas were not clearly identified and infiltrated.[1267, 1825, 1950] Equally good results were reported from injections of isotonic glucose solution (Ray [1439]). Elliott [518, 519] warned against the diagnostic use of infiltration: myalgia may arise in muscles supplied by an irritated root, which simulates fibrositis; therefore, relief from procaine does not exclude a root lesion. Dehydration gave relief in 13 and failed in nine of 22 patients with typical fibrositis (Copeman and Pugh). Intramuscular injections of neostigmine gave rapid relief in nine acute cases of cervical fibrositis and marked improvement in one of six years' duration (Kabat and Jones). [These nine acute cases were of "acute torticollis" or "stiff neck," which is almost always a short, self-limiting disease. Since many such cases are relieved spontaneously within a few days or even hours the results cannot be ascribed definitely to neostigmine.—Ed.] Some

tender spots responded well to freezings with ethyl chloride.[720] Of nine patients treated with bee venom, one was cured and eight "markedly improved."[69] Bogomoletz' "A.C.B. serum" was not helpful (Bach[48]). A stock streptococcic-staphylococcic vaccine was used by Crowe[410] on 89 children with "nonarticular rheumatism." "Profound changes in their well-being" presumably occurred.

Steinberg[1703, 1705] contended that vitamin E is necessary for the prevention and cure of the particular type of connective tissue change in primary fibrositis, the pathology being strikingly similar to that of nutritional muscular dystrophy in young rats; 143 of 145 cases were successfully treated by the oral or parenteral administration of tocopherol. It had no value in secondary fibrositis.[1700, 1702] Ant concluded that the direct application to the fibrositic site of vitamin E by inunction was beneficial, "apparently exerting a relaxant effect on muscle fibers, relieving tenseness and tautness and acting as a 'lubricant' to prevent tissue injury through hydremia." [The only case reported was one of frost-bite.—Ed.] But others considered the value of vitamin E for myopathies to be "purely speculative" (Mims[1247]) or psychotherapeutic (Milhorat[1238]). [The value of vitamin E in fibrositis or the myopathies remains uncertain.—Ed.] Deep roentgen therapy was considered useful in traumatic fibrositis.[1760]

An illustration of prevention was reported by Schmidt[1553] who studied the incidence of rheumatism in three coal mines and found no fibrositis (excluding lumbago) in one which had pit-head baths. [The statistical data given were too limited to permit an independent conclusion.—Ed.]

Miscellaneous Diseases of Muscles and Fibrous Tissue

Nocturnal Muscle Cramps. Night cramps in calf muscles occur with many conditions but especially with chronic (rheumatoid or osteo-) arthritis which was present in 40 per cent of Gootnick's 30 cases. Concentrations of calcium and phosphorus in blood were normal. The cramps, previously unrelieved by the use of calcium salts or aspirin, were promptly relieved in 90 per cent of cases by one daily (bedtime) dose of quinine sulfate (usually 3 grains; 0.2 gm.). The rationale was discussed.

Dermatomyositis; Polymyositis. Several cases were reported,[592, 668, 909, 1056, 1617] including two in Negroes in which detailed studies of skin were made (Irgang[898]). Hecht[804] reported five cases in children, with two deaths; four of these were complicated by calcinosis universalis. A case of "acute benign dermatomyositis" with recovery was noted (Leys[1096]). Among other manifestations described were mild fever, muscle tenderness, arthritic pains without localized swelling of joints, vasomotor phenomena and creatinuria.[804, 909, 1617] The similarity and relationship of dermatomyositis to other conditions with diffuse involvement of collagen (the "dermatoscleroses") were again considered but no new conclusions were presented.[71, 898, 1316] The lesions in skin and their differentiation from lupus erythematosus were discussed (Keil).

Localized or generalized involvement of skeletal muscles with nonsuppurative inflammation and degeneration of many fibers were constant findings. But these changes were not regarded as specific for the disease because of histologic variation.[909] Proliferation of sarcolemma nuclei and peripheral vascular changes were not uncommon.[1617] Indistinguishable lesions were found in acute rheumatic

fever, lupus erythematosus and myotonia dystrophica.[909] Jager and Grossman [909] considered the changes in muscle not unlike those seen by Curtis and Pollard (1940) [1h] in rheumatoid arthritis.

No new therapeutic measures were described. Creatinuria was reduced by the administration of fresh, vacuum-packed wheat germ, also by soy bean lecithin, but no effect on the dermatomyositis was claimed.[1239]

Scleroderma. Generalized scleroderma constitutes one of a group of diffuse collagenous diseases of unknown etiology, which includes dermatomyositis, disseminated lupus erythematosus, acrosclerosis (Klemperer, Pollack and Baehr [1016]). "Striking similarities in the detailed pathology of these various conditions require evaluation for a possible relation or common denominator" (Banks [71]). To replace "scleroderma" the term "progressive systemic sclerosis" was proposed, as scleroderma is only part of a systemic disease, the most serious lesions of which actually occur in viscera (Goetz [660]).

In extremities stiffness in joints and muscles, tendon contractures, osteoporosis and arthropathy with absorption of the bones of digits develop.[136, 1908] Deposition of calcium salts is likely in subcutaneous tissues, particularly in regions subject to pressure.[274, 660, 903, 944, 1786, 1908] Generalized scleroderma and acrosclerosis were distinguished sharply; the latter was related more closely to Raynaud's disease (O'Leary [1316] and Waisman).

Described were the pathologic lesions in skeletal muscles,[136, 1908] arterioles, collagen tissue,[136, 1278, 1397] lungs, heart, esophagus, gastrointestinal tract and kidneys.[136, 660, 737, 903, 1278, 1397, 1419, 1908]

There is no specific treatment.[491]

Calcinosis. Calcinosis occurs alone [1136, 1356] or in association with scleroderma,[127, 274, 660, 903, 944, 1786, 1908] acrosclerosis [1317] and dermatomyositis.[80, 804] Differentiation of the two types, namely, calcinosis circumscripta and calcinosis universalis, is applicable only to characteristic examples; individual cases are frequently indeterminate.[1786] Serum calcium and inorganic phosphorus were normal.[80, 274, 944, 1308, 1356, 1786] Consistently elevated blood uric acid was reported in one case.[1356] Abnormal calcification in muscles of forearm, as found in devitalized tissue, was discussed.[1585]

Treatment has been unsatisfactory. No improvement from sympathectomy was observed (Nuñez and Arthur [1308]). Unilateral parathyroidectomy was of little value in one case (Byron and Michalover [274]), beneficial in another in which many calcific deposits disappeared (Bartels and Catell [80]).

Arthrogryposis Multiplex Congenita. This embryonic malformation is best explained by arrest of normal embryonic development. The term means a crooked joint. However, the contractures of joints are secondary, the initial lesion being a primary aplasia or hypoplasia of certain muscle groups. Other terms used have been "amyoplasia congenita" or "myodystrophia foetalis deformans," to indicate that the deformities result from fatty degeneration of muscles during intrauterine life. Features include articular rigidity, congenital defects (club foot or hand, dislocated hips), abnormal posture, poorly developed muscles. Eighteen children described had "a stuffed sausage-like appearance," little palpable muscle, periarticular thickening and contractures (Katzeff). Histologically atrophy and fat replacement of involved muscles occur. Treatment included manipulations with or without anesthesia, supports, surgical corrections; definite improvement resulted (Katzeff; Badgeley [51]).

Miscellaneous Conditions

Herniations of Subfascial Fat. These were found by Copeman and Ackerman to be the cause of certain cases of "backache" or of supposed "fibrositis" of muscles of back. In characteristic regions, especially about the lumbar, gluteal or episacroiliac regions of soldiers with supposed "fibrositis," painful trigger points or myalgic spots were discovered, sometimes also tender subcutaneous "rheumatic nodules." To determine their nature the backs of 14 soldiers who died of various causes were dissected. A "basic fat pattern" was discovered which coincided with the regions in which "fibrositic pain" and nodules had occurred in life. But instead of finding subcutaneous fibrous nodules Copeman and Ackerman found small herniations of lobulated fat penetrating through fascial tears (weaknesses, deficiencies) or through the unprotected foramina by which the posterior primary rami of the first three lumbar nerves pierce deep fascia. The fat protruding was pedunculated, nonpedunculated or foraminal. Pain was ascribed to edema in the lobules and tension which may lead to herniation if fascial walls are deficient. At necropsy the bubbles of fat, found in the lumbar region, could be converted into tiny hernias by pressure on adjacent tissue. Conversion from bubbles to true hernias during life was attributed to incidents such as sudden trauma, sudden flexing of back or prolonged rest in the supine position.

Tender subcutaneous nodules were removed surgically from 20 patients with localized or disseminated back pain and proved to be herniated fat with no evidence of inflammation; hence such hernias were believed the cause of "trigger zones" in certain cases of supposed fibrositis. In later cases Copeman and Ackerman used more conservative treatment. Overlying skin was anesthetized, the nodule was transfixed with a cutting needle from which 10 to 20 c.c. procaine solution was injected; the needle was then swept around to undercut the nodule and thereby to disperse edema and tension. The pain and tenderness of the pre-existing "fibrositis" were often thus relieved.

Further anatomic and clinicopathologic studies were made by Mylechreest who successfully treated four patients by surgical removal of herniated fat and also by Herz who similarly relieved six patients with severe subacute or chronic backache.

[In the past certain physicians, including some of us, have often felt low on the back, especially in the sacroiliac region, tender or nontender nodules of different sizes which were suspected of being subcutaneous fibrositic nodules, clinically active or inactive. But when certain nodules were removed only fatty tissue was present and their nature was not understood even though some patients were curiously relieved of symptoms. Thus in 1935 Sutro found such nodules in sacroiliac regions in 55 per cent of 170 unselected hospital patients, a third of whom had low back pain. He removed some nodules but found only noninflamed fat and considered them "protective buffer pads" unrelated to symptoms despite the relief in some cases. In 1937 Ries found "episacroiliac lipomas" in 317 (32 per cent) of 1,000 patients examined therefor: in 18 per cent of 250 males, in 36 per cent of 750 females. Of the 317 patients with tumors 150 had backache, 167 did not; 231 had bilateral, 86 unilateral tumors. The tumors were "spontaneously painful" in 131, painless in 186 cases. Of the 1,000 persons 309 had lumbosacral backache; 150 with, 159 without tumors. The backache was near the sacroiliac joint with slight radiation. "Some 20 patients" with sensitive

tumors and backache were treated by excision of, or injections of procaine into, the tumors with permanent relief in some, only temporary relief in others. The excised tumors were of encapsulated fat. The pathogenesis was not determined. More recently Buckley wrote [243]: "Quite frequently small masses of fat are regarded as fibrositic nodules" and Collins [358] found three "typical fibrositic nodules" on removal to be "noninflamed lobulated fat with fibrous encapsulation," "simple lipomata."

The nature of at least some of these subcutaneous "nodules" now is more clear. Recently Copeman and Ackerman (1947) and Herz (1946) [837] reported further results from conservative or surgical treatment. The earlier papers of Copeman and Ackerman and of Mylechreest were entitled "Fibrositis of the back" even though the fatty tumors were not fibrous and were obviously not the orthodox "fibrositic nodules" and though the symptoms were proved not to be due to fibrositis. This unfortunate error in terminology was corrected in recent papers. Although we believe these are important reports we must remark again that many such nodules are essentially painless, and some tender ones may not be the cause of the patient's symptoms. We hope that these "new" fat herniations will be handled temperately and not removed uselessly and overenthusiastically. It is premature to conclude now that all tender subcutaneous nodules are fatty herniations or that such fatty (not fibrous) nodules explain most "fibrositis." But these studies constitute an important new approach to the vexing problem of backache.—Ed.]

Psychoneurotic Musculoskeletal Symptoms; "Psychogenic Rheumatism." *1. Definition.* "Psychogenic rheumatism" must not be confused with organic rheumatic disease (rheumatoid arthritis, rheumatic fever, gout) influenced by predisposing, precipitating or aggravating neurogenic or psychogenic factors. Some physicians state that (1) certain persons inherit a "personality type" which makes them susceptible (inherited susceptibility) to the development of organic rheumatic disease [487, 744, 745, 747, 1346]; or (2) a normal person may run into chronic emotional stress sufficient to alter his neuroendocrine system, "lower his vitality" and make him susceptible (acquired susceptibility) to organic rheumatic disease; in some such people a serious emotional crisis may appear to precipitate the onset of rheumatoid arthritis [1346]; or (3) in a given case the course of an organic rheumatic disease, such as rheumatoid arthritis, is influenced for better or worse by the occurrence or disappearance of emotional stresses.[744, 1346, 1467, 1751] These circumstances suggest a neurogenic or psychogenic origin of organic rheumatic disease but the resultant disease is *not* psychogenic rheumatism.

Psychogenic rheumatism consists of musculoskeletal symptoms of a purely functional or psychoneurotic type without organic lesions. It is of two forms: primary and secondary. In the primary form (in which no organic rheumatic disease is present) psychic stress is the sole cause of musculoskeletal symptoms which may masquerade as true rheumatic disease; examples are functional "aches and pains" from musculoskeletal tension simulating fibrositis, hysterical contraction of hand or knee simulating rheumatoid arthritis, hysterical flexion of spine (camptocormia) simulating spondylitis. In the secondary form psychic stress produces musculoskeletal symptoms superimposed on a recently healed (functional prolongation) or a currently present and often relatively minor rheumatic disease (functional overlay).

This condition as it appears among civilians has been described vividly by Halliday,[743, 747] but has been brought to the fore chiefly by recent military experiences excellently summarized by medical officers.[173, 174, 524, 571, 581, 802, 890, 1544]

2. Terminology. No entirely satisfactory name has been coined. It is, of course, "psychoneurosis manifested by musculoskeletal symptoms," but for daily use a less cumbersome, shorter term is required. Various terms have been used: "psychogenic rheumatism," [173, 174] "psychoneurotic or psychosomatic rheumatism," [743, 1627] "psychoneuroendocrine disorder with fibrositis as a dominant physical symptom," [743] "psychogenic fibrositis," [978] "arthralgia," [802] "neurotic or hysterical joints," "functional or psychogenic muscular disability," [1467, 1544] "hysterical 'fibrositic' complaint," [524] "psychogenic back pain," [1538] "psychalgia." [1975] Flind and Barber [571] preferred the psychiatric term applicable to each case: "hysteria (or anxiety or depression) with so-called rheumatic pains." Each term has objectionable features; until a better one appears, "psychogenic rheumatism" will serve if physicians understand that it connotes no *organic* rheumatic disease produced by psychic factors.

3. Incidence. Psychogenic rheumatism affected a third of insured patients with "chronic nonarthritic rheumatism" studied by Halliday,[743] 35 per cent of 120 "rheumatic patients" at a Royal Air Force rheumatism center (Flind and Barber [571]), half of 50 patients with supposed "fibrositis" (Ellman and colleagues [524]), all of 26 Canadian soldiers with "arthralgia" (Heaton [802]). It affected a third of 450 American soldiers who had "arthritis or allied conditions" studied by Boland and Corr [174] at an army general hospital, being the commonest cause of disability.[173, 174] At another American army general hospital 50 per cent of patients admitted for organic neurologic disease really had "functional muscular disability" (Saxe [1544]).

4. Clinical Data. In a minor percentage of cases it took the form of hysterical contractures of extremities with bizarre postures, gaits or limps[173, 174, 571, 802, 1130, 1538] or contractures of spine (camptocormia).[748, 1531, 1905] Of 100 psychiatric soldiers 15 per cent complained of "backache." [144] The great majority of such cases were cases of arthralgia or myalgia or both, usually misdiagnosed as "arthritis," "fibrositis" or "backache." [581] Of 269 psychoneurotic patients studied by Friess and Nelson [615] 57 (21 per cent) complained chiefly of musculoskeletal symptoms ("pains" in muscles more often than joints). All had previously received an erroneous diagnosis and treatment of "arthritis." After a five-year follow-up, there was still no objective or laboratory evidence of organic disease. Chronic fatigue is now recognized as one of the chief symptoms of nervous exhaustion and maladaptation (Kepler). Thus the symptoms of "psychogenic rheumatism" were chiefly of the "skeletal muscle pattern; simple derivatives" were fatigue, weakness, stiffness, drawing sensation, aching (Garner). From the psychiatric standpoint most of the reactions in one group were classified as of the hysterical form with the "resentful" type more common than the "histrionic" or "ailing" type.[524] But of Flind and Barber's 42 cases [571] reactions were of anxiety type in 52 per cent, hysterical in 41 and depressive in 7 per cent. Halliday [743, 747] and Fox [581] interpreted the symptoms largely in terms of symbolism. Thus lumbago or "backache" symbolized resentment, resistance, threats to pride. When rigid, stiff or touchy people become ill, "the rigidity, stiffness and wincing responses of rheumatism" develop. Left-sided pain relates to "sinister" feelings of loss; pains in extremities "may symbolize repressed desires to attack"; "left shoulder neuritis" so often is "a neuritis of deprivation, not of vitamins but of a married partner or other dearly beloved person or object." But Abrahams hesitated to accept such a symbolic interpretation of "fibrositis." Regardless of their pathogenesis or meaning the pains are more real than generally believed; as Kelly stated [978]: "Psychogenic pain

should not be divorced from reality, for all pains are peripherally induced and subjectively appreciated."

5. Etiology. Among soldiers the precipitating factors included the conflicts, frustrations and dangers incident to military service (Boland and Corr), but most of them had demonstrated psychoneurotic reactions from childhood (Flind and Barber [571]; Heaton [802]). Thus the remote factor of unstable personality plus the immediate precipitating factor of an (to them) intolerable situation combined to produce symptoms which largely represented an escape mechanism, a flight into illness. Boland and Corr observed that a history of rheumatic disease sometimes provided a suggestion which the psychoneurotic unconsciously adopted to suit his purposes. The emotionally unstable person will elevate a minor intermittent (rheumatic) discomfort to the status of a major disability.[802] One of Heaton's [802] patients used a genuine (but minor) disability of knee "for more than it was worth" for a year; then when rebuked for this he had multiple pains without discoverable organic basis. Thus a harmless crepitation of knee or a knuckly finger may be offered by the psychoneurotic as bona fide evidence of organic rheumatism to explain widespread functional complaints.[571]

6. Diagnosis. Methods of diagnosis were carefully described and included the type of past history usually found, previous attacks of conversion hysteria of nonrheumatic type, personality appraisal, physical examination including study of face and manner,[746, 1467] absence of significant evidence for organic disease.[174, 571, 743, 746, 747, 1130, 1544] Muscle analyses demonstrated hysterical overreactions, overdramatization of affected parts, writhing, groaning, lack of consistency of painful motions.[571, 1130, 1544] Electrical testing gave useful confirmation.[1544] An abridged psychiatric examination suitable for practitioners was described.[524, 571, 743, 746] Narcosynthesis involving intravenous injections of pentothal or amytal proved most useful.[1544] The differentiation of psychogenic rheumatism from "true fibrositis" [571, 743, 747, 802, 1627] and from malingering [174, 571] was described. "Iatrogenic (physician-induced) rheumatism" might be defined as the psychogenic rheumatism mistakenly called "organic rheumatic disease" by an unwary physician. " 'Fibrositis' is apt to be the physician's escape from reality" (Heaton [802]). A mistaken diagnosis is serious as it represents an "authoritative affirmation to the patient of a nonexistent condition" (Saxe [1544]).

7. Treatment. These included "explanation, persuasion and re-education." [571] Symptoms often disappeared during or after narcotherapy.[1544] Physical therapy was of little or no value [802] and the pains should not be treated per se because "they merit no more special attention than the tachycardia of an anxiety state" (Flind and Barber [571]). Camptocormia among soldiers was sometimes successfully treated by narcotherapy or the "tilt-table treatment," [1905] by postural training,[748] less often by suggestion. But in some cases the only "cure" was discharge from the army.[1531] In civilian life psychotherapy is often successful but, despite explanation and persuasion, symptoms often continue until the irritating situation is improved (Halliday). Despite psychotherapy most of the patients of Friess and Nelson [615] after a lapse of five years had the same complaints as before. "This fixity of the complaint is but one manifestation of the basic changelessness of the psychoneurotic patient and probably represents his most outstanding characteristic." In the treatment of chronic fatigue

and nervous exhaustion the proper ratio of work, worship, play and love is of profound importance (Kepler). Because psychogenic rheumatism is not a precursor or "forme fruste" of organic rheumatism these patients are not especially liable to develop arthritis later despite their severe and persistent psychogenic rheumatism.[802]

The Shoulder-Hand Syndrome. This was discussed under "The Painful Shoulder."

Disseminated Lupus Erythematosus. Unusual interest in this disease was reflected by the publication of 52 reports with many general discussions during the period of this review.[64, 94, 178, 318, 483, 624, 625, 821, 981, 1144, 1163, 1166, 1167, 1168, 1178, 1209, 1434, 1581, 1635] The name, "subacute nonrheumatic arthroserositis," was proposed (Proger). Etiology still remains a mystery. Considerable support was expressed for its allergic nature.[281, 583, 1398, 1731] The antigens suggested were sulfonamide-protein, actinic rays, transfused blood and horse serum; Fox [583] wondered if this malady might be in the nature of chronic serum sickness.

The vascular and perivascular lesions which characterize this disease were described.[71, 940, 1416, 1579] These arteriolar changes are the common denominator of lupus erythematosus, scleroderma, dermatomyositis, Libman-Sacks syndrome and periarteritis nodosa. In earlier papers Klemperer, Pollack and Baehr [1016, 1017, 1018] considered lupus erythematosus primarily a vascular disease, but recently they emphasized that the fundamental pathology is a widespread damage to the collagenous tissues of which the vessels are only a part. The characteristic organic changes are local manifestations of widespread fibrinoid degeneration of collagen, a biophysical change which results in derangement of this extensive colloid system ("organ"). Patchy pulmonary inflammatory infiltrations,[1429] hypereuglobulinemia [335, 1776] and false positive Wassermann reactions were noted.[1391] Keil compared the lesions of skin and mucous membrane with those of dermatomyositis. Lesions of the central nervous system and resulting symptoms were described.[425]

Of note was the common occurrence of arthralgia or of acute or chronic arthritis. Articular pain and stiffness, sometimes swelling and limited motion were prominent at times during the illness in most of the new cases reported. Often the articular symptoms constituted the chief complaint; many times they appeared weeks or months before the skin lesion.[64, 71, 287, 318, 327, 335, 425, 483, 583, 714, 883, 908, 1016, 1163, 1166, 1168, 1179, 1354, 1391, 1416, 1429, 1434, 1446, 1579] "Migratory evanescent arthritis" occurred in 23 (77 per cent) of 30 cases.[335] Articular symptoms may last six months to six and one-half years.[714] In some cases the articular involvement resembled rheumatoid arthritis [1168]; indeed such a diagnosis was sometimes erroneously made.[908] Permanent articular changes are rare [1168] but deformities, involving small joints and usually appearing late, have been reported.[327]

The "rheumatic symptoms" of disseminated lupus were contrasted with those of periarteritis nodosa; in the former, symptoms are generally articular, less often muscular,[287, 318, 483] whereas in periarteritis nodosa the pains are more likely to be muscular or neuritic than articular since polymyositis and polyneuritis of peripheral type are common.[71, 1163]

Pathologic studies of affected joints have been meager.[327] In one case "marked synovitis but no evidence of rheumatoid arthritis" was noted.[1163] In two of six other cases "synovial joint changes" were found but not described (Guion and Adams). In another case of swollen painful joints no articular

pathology was found at necropsy (Bauer and MacMahon). Hypertrophy of synovial villi, inflammation with perivascular infiltration in subsynovial and capsular tissues, formation of subperiosteal bone and hyperplasia of synovium have been previously reported (Cluxton and Krause).

[It is regrettable that joints were so rarely examined at necropsy even in those cases in which articular symptoms were dominant early features. From 60 [1h] to 77 per cent [335] of these patients have symptoms which may resemble periarticular or intramuscular fibrositis, subacute or chronic rheumatoid arthritis or even acute rheumatic fever. Recent studies in fatal cases gave minute details of practically all bodily tissues including brain, bone marrow, even tongue and eyes, but not joints. Apparently the synovial cavity is the "last frontier" for most pathologists. Let us encourage appropriate necropsy studies in fatal cases in which articular symptoms are notable.—Ed.]

Treatment remained a problem. Articular lesions generally do not respond well to treatment.[327, 1579] Cures of the disease with sulfonamides were reported,[863, 1354] but some physicians [1398] cautioned that sulfonamides might produce untoward effects. Liver extract was considered helpful [388, 1003]; treatment with iodine [287] and removal of "foci" of infection were advised.[1677, 1792] Sosman stated that "spray roentgen-ray therapy has given very promising results." A seven-year recovery from acute disseminated lupus erythematosus without special treatment was reported in a male child (Horstmann). Aurotherapy was still considered "the most efficacious remedy" by Bechet.

Periarteritis Nodosa. For this disease some physicians preferred the terms, "primary arteritis" [964] or "polyarteritis." [1143, 1696]

1. Etiology. This has been attributed to virus, different bacterial agents, toxins and disease of central nervous system, but the likelihood that it is due to hypersensitivity was strongly suggested by Rich [1456, 1457, 1458, 1459, 1460] who noted the development of periarteritis nodosa in patients shortly after they had serum sickness, hypersensitive reactions to sulfonamides or iodine. Apparently substances of widely different chemical nature may cause this destructive vascular disease by their ability to induce anaphylactic hypersensitivity. Rich [1460] produced, experimentally in rabbits, typical diffuse periarteritis nodosa by a condition analogous to human serum sickness. Development during thiourea therapy was reported in one case (Gibson and Quinlan) and thiouracil produced "periarteritis nodosa-like" lesions in rats (Marine and Baumann). But McCall and Pennock [1183] could not correlate the disease in 10 cases with previous sulfonamide therapy. By giving large overdoses of desoxycorticosterone acetate Selye and Penz produced vascular lesions in rats similar to those of periarteritis nodosa, malignant hypertension and rheumatic fever. Lesions of periarteritis nodosa also were noted in two cases regarded clinically as cases of trichinosis, with trichinellae in muscles. Trichinosis, with its strong allergic manifestations, also may be a cause of this arterial disease (Reimann, Price and Herbut [1449]). In another case periarteritis nodosa and encysted trichinellae were found at death (Banowitch, Polayes and Charet).

2. Clinical Data. Numerous studies appeared.[58, 196, 272, 558, 959, 1089, 1100, 1105, 1133, 1171, 1242, 1274, 1571, 1669, 1696, 1720, 1789, 1876, 1957] The disease affects four males to one female.[1579] Cases in children [337, 1562] and in an infant one month old were noted.[1934] Clinical features were reviewed: variable fever and leukocytosis with a wide variety of symptoms depending on which, or how much each, system is affected by the diffuse arteritis, the usual order of frequency being lesions in

kidney, heart, gastrointestinal tract, mesentery, liver, muscles, nerves.[550, 1184, 1579, 1677] Common in some cases were fever, leukocytosis, eosinophilia and asthma [149]; in others fever, nephritis or intestinal symptoms, polyneuritis and polymyositis.[73] A notable eosinophilia occurs in 10 to 14 per cent of cases.

Muscles are affected clinically and pathologically in 30 to 35 per cent,[1579, 1677] joints less frequently. In recent cases early symptoms were muscular aching and tenderness either localized (in calf, leg, neck) or widespread,[73] muscle pain of varying intensity (at times sufficient to prevent standing or use of an extremity),[73, 667] muscle spasm,[550] cramps, atrophy,[73, 558] sensory changes in extremities (weakness, numbness, tingling, "pins and needles"),[73, 550] painful clumsy motion (dysarthria).[1147] All these result from polymyositis and polyneuritis. Myalgia affected 64 per cent of Jones's cases,[919] all of McCall and Pennock's.[1184]

Articular symptoms of other patients were "painful feet," [1562] pain in wrist without redness or swelling,[73] painful shoulders,[141] painful swollen ankles,[1353] weakness and wasting of hands,[550] painful knees, wrists and elbows.[667] One case in which febrile polymyalgia with swollen ankles and arthralgias elsewhere were present resembled a case of "rheumatic fever." [558] "Arthritis (pain and/or swelling)" occurred in 57 per cent of Jones's 14 cases.[919] Pains in muscles or joints affected all of 12 adult patients,[1184] 50 per cent of 44 children.[964] Tenderness, weakness and soft pitting edema of legs affected three patients.[1143]

Pathologic studies of muscles at biopsy or necropsy showed minute foci of "chronic interstitial myositis," [558] "angiomyositis," [919] healed panarteritis in pectoral muscle or mild periarteritis of orbital muscle,[73] periarteritis and patchy degeneration of adjacent muscle fibers.[1147] Biopsy of muscle was "positive" for periarteritis nodosa in five of Jones's nine cases but it often shows only "nonspecific focal myositis." [558] Joints, bursae and tendon sheaths may reveal granulomatous, not just vascular, lesions.[959] Bauer [1166] reported on one patient with "marked synovitis"; typical vascular lesions of periarteritis nodosa affected synovial blood vessels.

Special features (unrelated to muscles or joints) were discussed.[141, 195, 825, 1143, 1147, 1562, 1889, 1895] In one case the vascular process was healed,[149] but the "healing" results in a progressive, irreversible ischemic process which causes death, generally by renal damage.[1183]

Diagnostic aids included biopsies of muscle or periarteritic nodule, the presence of a "unique urine" (erythrocytes, red cell casts, oval fat bodies, fatty and broad casts, excess protein) [1035] and sigmoidoscopic detection of characteristic intestinal lesions.[550] Periarteritis should be considered in any chronic illness [73] especially with obscure sepsis, vague abdominal symptoms, polymyositis, polyneuritis, wasting, renal insufficiency, hypochromic microcytic anemia and eosinophilia.[1801] The similarities and differences between periarteritis nodosa and disseminated lupus erythematosus were discussed,[71, 1163, 1166] also the possible relationships with rheumatic fever.[558, 919, 959, 964, 1183, 1184]

In certain cases features suggestive of trichinosis were present (muscle pains, eosinophilia, periorbital edema) [1571]; in others periarteritis nodosa and trichinosis coexisted, perhaps causally.[1449]

3. Treatment. This is unsatisfactory; the disease is usually fatal. Most writers considered therapy only supportive. An apparent cure with sulfapyridine was noted [667] but others considered sulfonamides useless.[1184] "Spray roentgen-ray therapy may be of some benefit." [1677]

Sarcoidosis; Benign Lymphogranuloma. Sarcoidosis or benign lymphogranuloma is a generalized disease that may involve any organ in the body; it

thereby produces many clinical syndromes. Granulomatous lesions of skin were called "lupus pernio"; characteristic changes in bone were named "osteitis tuberculosa multiplex cystoides"; ocular lesions, parotitis and facial palsy was called "uveoparotid fever." But these are all parts of one disease; other synonyms are Boeck's sarcoid or Besnier-Boeck-Schaumann syndrome. The history of the disease was reviewed.[585, 955]

1. Clinical Data. Lymph nodes, lungs and bone are most often affected. Bone lesions affect 10 to 20 per cent of cases; those in the 10 cases of Katz, Cake and Reed [955] were usually in phalanges, metacarpals and metatarsals. Joints per se are not involved but arthralgia may occur.[955] Circumscribed cysts are the most common osseous lesions but a reticulated appearance with thickened trabeculae and rarefaction of surrounding bone may occur; swelling and deformity, mutilation or even amputation may result.[769, 955] Sarcoid tissue may produce tenosynovitis, intramuscular nodules and subcutaneous tumors (Frank [585]).

Thirty-two cases were reported.[484, 585, 769, 955, 1201, 1395, 1516, 1740, 1797] Clinical and postmortem findings in 43 cases were collected from the literature (Rubin and Pinner). There are few constitutional symptoms: sometimes weakness, fatigability, anorexia, loss of weight or arthralgia occur. Symptoms are caused by mechanical interference with the function of organs, not by intoxication. Sarcoid lesions exert pressure on normal tissue and thus displace or destroy it.[955]

Serum calcium is normal or slightly elevated; alkaline phosphatase is increased.[1740] Plasma globulin and sedimentation rates may be elevated.

2. Differentiation. The osseous features of sarcoidosis must be distinguished from tuberculous dactylitis, osteomyelitis, gout and rheumatoid arthritis. The distinction between "osteitis tuberculosa multiplex cystoides" (sarcoidosis of bone) and multiple cystic tuberculosis of long bones was discussed: in the former the tuberculin reaction and tests on guinea pigs usually are negative; there occur slow healing, honeycombed areas of bone rarefaction without periostitis, fibrosis or sinus formation, rarely involvement of long bones, frequent involvement of skin (lupus pernio) or lungs (Sweet and Abramson).

3. Etiology. The idea that this is a benign form of tuberculosis was not generally supported by recent writers. The presence of neutropenia and leukopenia suggested to some [955] that a virus was responsible but others disagreed.[484] Although most patients with erythema nodosum have no pulmonary signs or symptoms, Kerley [985, 986] often found massive enlargement of bronchial glands with or without infiltration of lungs. From a study of 37 such cases he concluded that erythema nodosum with visceral lesions represents sarcoidosis: "It would appear that 'erythema nodosum-sarcoidosis' in Europe and 'erythema nodosum-coccidioidomycosis' in California are, if not the same disease, closely related."

4. Treatment. Roentgen therapy to lungs was helpful in most of 14 cases.[1395]

Painful Osteoporosis; Causalgia; Nontraumatic and Posttraumatic Osteoporosis (Sudeck's Atrophy). Painful osteoporosis may be posttraumatic or nontraumatic. The former is more common and has followed contusions, sprains, fractures, bites and burns of mild or severe degree. Less common is postoperative painful osteoporosis from the "trauma" of a simple uninfected surgical procedure. In Buchman's case [236] one week after surgical treatment of stenosing tendovaginitis of the thumb a painful stiff hand, wrist and shoulder with swelling, heat, duskiness of hand, painful stiffness of hand and shoulder, spotty rarefaction in roentgenograms of fingers and wrists and to a lesser degree

in elbow and shoulder developed. After 18 months the condition slowly disappeared. In another case, reported by Brown,[222] a foot was affected after a sprain and was relieved three months later by lumbar sympathectomy.

The cause is unknown but involves a vasomotor disturbance which produces hyperemia in bone, increased vascularity, thinning of bone lamellae and filling of the interlamellar spaces with fibrous tissue. Hyperemia in soft tissues produces duskiness, edema, local heat, periarticular thickening and limited motion. The circulatory disturbances are presumably functional in nature, sympathetic in origin. Normally every trauma evokes an immediate vasoconstriction of the injured part which soon gives way to vasodilation. If the latter persists, painful osteoporosis may result. "The paradox is that a sympathectomy which of itself increases vasodilation, usually brings immediate relief": so wrote Buchman.[236]

1. Pathogenesis. The syndrome somewhat resembles the "shoulder-hand syndrome" already described; the two may be closely related although the former is supposedly related to hyperemia, the latter to ischemia. An explanation of painful osteoporosis was offered by DeTakats in two informative papers [463, 464] which we will review in some detail because of their importance.

Sudeck's atrophy, Lériche's posttraumatic osteoporosis, Weir Mitchell's causalgia, peripheral trophoneurosis, reflex dystrophy and chronic traumatic edema all result from the same mechanism. Certain nontraumatic irritative lesions in any of the three sensory neurons which are capable of producing chronic spreading hyperalgesia also will invoke this mechanism. The location and anatomic connections between the first, second and third order (sensory) neurons was described. Lesions of the first sensory neuron are produced not only by various types of trauma but also by certain diseases such as periphlebitis or lymphangitis. Apoplexy of cauda equina, poliomyelitis, tabes, syringomyelia and other diseases may produce lesions of the second (higher) sensory neuron. Cerebral thrombosis, infarcted cortex with painful hemiplegia, brachial plexus injuries constitute lesions of the third (highest) sensory neuron. Peripheral trauma activates the first (lowest) neuron producing vasomotor reflexes which under certain conditions are predominantly vasodilator. The trauma which induces causalgia results, not from major injuries to bones, joints, nerves or blood vessels, but usually from minor injury (sprains or minor fractures) to foot, ankle, hand or wrist. Thus the character of the initial trauma allows no prediction as to its late sequelae. The trauma producing Sudeck's atrophy seems to activate both vasoconstrictor and vasodilator fibers with dominance of vasodilators. This produces increased capillary pressure and stimulation of sensory receptors with the resultant throbbing, burning pain of causalgia. Lewis (1936) postulated the secretion of a pain substance at the termination of nerve fibers belonging to the posterior root system. (Since these fibers were neither sensory somatic nor sympathetic fibers, he named them "nocifensor nerves.") It is not clear whether the substance produced at the nerve endings is acetylcholine or histamine; both have been recovered after stimulation of posterior root fibers. In irritative lesions in any of the three sensory neurons a group of fibers is activated which secrete pain-producing, vasodilator substances at nerve endings. In the causalgic state (unlike other painful states which lead to continuous afferent impulses) there is an efferent stimulation of pain-producing vasodilator substances which, unless blocked or neutralized early, will lead to the sensitization of higher and higher levels.

Three stages of the syndrome were mentioned by DeTakats.[463, 464] Features of the first stage include severe persistent burning pain, paroxysms produced by jarring, air currents or emotional upsets, warm dry extremity, edematous subcutaneous and periarticular spaces, spastic muscles attempting to splint wrist or ankle, increased cir-

culation to the injured part as shown by blood flow and oscillometric curves. In this stage pain remains limited to injured site; osteoporosis is absent since hyperemia for four to six weeks is necessary for its production. In this stage the process may cease to develop or be combated by adequate treatment.

If not, the second stage appears and includes spreading periarticular edema, less warmth and flushing, cyanosis, cold and hardness of affected part, stiffening of joints, muscular atrophy, spotty osteoporosis, a less active blood flow but with more vasodilation in the affected than in the uninjured limb, a painful spreading neuralgia or hyperalgesia which may defy segmental distribution. In this stage the condition is still amenable to treatment.

In the third and final stage there occur progressive atrophy of skin, muscles and bone with extensive osteoporosis of nonspecific appearance, intractable pain spreading to the root of a limb or even to the trunk.

The feature of osteoporosis has been overstressed; a diagnosis of Sudeck's atrophy cannot be made on roentgenograms alone. In the early stage, osteoporosis may be absent; later when osteoporosis is at its height, the syndrome may be subsiding. When coarse trabeculation occurs with signs of recalcification the peak of the syndrome is passed. Pain does not parallel osteoporosis: after treatment pain may subside rapidly despite persisting osteoporosis.

2. Treatment. Early appropriate treatment is important; of crucial importance is an understanding of which sensory neuron is affected (DeTakats [463, 464]). The first neuron lesion, if unrecognized or mistreated, may within 10 to 30 days ascend to the second neuron level and produce the same diffuse intractable dysesthesia with mirror images to contralateral symmetrical areas. The early causalgic state (burning, throbbing pain relieved by suprasystolic compression of limb, by elevation, cooling or moisture) is still localized to the area of stimulation. At this stage the site of trauma (digit, ankle, wrist) should be immobilized and thoroughly infiltrated daily with 1 per cent solution of procaine which blocks sensory stimuli and inhibits secretion of the vasodilator substances. The involved nonmyelinated fibers are more sensitive to procaine than the large myelinated sensory fibers and remain paralyzed even though the anesthesia wears off shortly.

If pain is not relieved, the stimulus has progressed to a higher level as often is shown by spreading neuralgia and osteoporosis. Then repeated block of paravertebral sympathetics is advisable, often with much relief.

Although sympathetic block of itself produces vasodilation, it relieves the painful vasodilation of causalgia because the causalgic type of vasodilation differs from that produced by heat, vasodilators or sympathetic block. The vasodilation with Sudeck's atrophy is not due to sympathetic efferent fibers since sympathectomy not only does not abolish it but increases it. Since sympathetic block helps to relieve the pain of lesions of the second neuron, this pain like that from peripheral traumatic lesions to the lower, first neuron, must be due to a secretion of painful substances which the improved circulation neutralizes. Sympathetic block accelerates blood flow, opens arterioles but constricts capillaries, and gives striking relief despite increased vasodilation. The reflex vasodilation, which is invariably present just after trauma, produces tissue acidity which inhibits destruction of acetylcholine and modifies nervous impulses. Sympathetic block produces a shift to the alkaline side so that acetylcholine is rapidly destroyed. Injections may be required daily or only once a week.

If sympathetic block fails to relieve pain, sympathectomy will be of no value. But if the block promptly abolishes symptoms and they recur with undiminished in-

tensity after a few hours or days, sympathetic ganglionectomy should be performed immediately according to De Takats:[463, 464] for an upper extremity, infiltration or removal, not of stellate ganglion but of second and third ganglia, is required; for a lower extremity, removal or infiltration of the second and third lumbar ganglia.

In late severe cases the spreading neuralgic pain is intractable, may involve shoulder, thoracic wall or opposite limb and may be associated with severe psychoneurosis from unrelieved pain for which psychotherapy is required. For late contractures and ankylosis orthopedic measures are necessary. If local infiltration, peripheral nerve block, sympathetic block and spinal anesthesia fail to give relief, tractotomy at different levels is indicated and DeTakats recommended cutting of spinothalamic tract (anterolateral chordotomy) for intractable lesions of the second level; possibly cerebral tractotomies or removal of sensory cortex for lesions of the third level; "the latter may seem desperate measures" but patients with lesions of the third level become drug addicts, have severe personality changes and often commit suicide and at this third stage neither section of posterior roots nor chordotomy is of value. DeTakats gave the results of these various treatments in 36 cases of "Sudeck's atrophy."[463]

[A newly recognized type of painful osteoporosis with periarticular swelling, which should be known to rheumatologists, occurs as a complication in 2 per cent of hypertensive patients treated with potassium thiocyanate. Eleven cases were recently reported by Hinchey, Hines and Ghormley. Three to six months after such treatment was begun, painful osteoporosis appeared, then mild or moderate dusky periarticular swelling. Feet and ankles were affected most often, a hip, knee or wrist sometimes. One of us, P. S. H., has seen three patients who were referred because of "atypical rheumatoid arthritis." Following discontinuance of doses of the drug recovery began in two or three months, was complete in all 11 cases within five to seven months.—Ed.]

Ganglion. A ganglion is a cystic swelling usually near a joint or tendon sheath which contains thick mucinous fluid. Its lining closely resembles that of joints or bursae. Although bursae are usefully placed, ganglia "have been donated to us by nature as an effect without a known cause." Their origin and nature are in dispute: a ganglion has been considered a rupture of tendon sheath, a retention cyst, a neoplasm, a herniation of tendon sheath or, the more commonly accepted view, the result of cystic degeneration (fibroplasia and colloid degeneration) of connective tissue around, but not inside, the joints.[312, 1442] Trauma is not a constant etiologic factor. Reportedly 58 per cent of ganglia disappear spontaneously (Cherry and Ghormley[312]).

Numerous treatments have been used such as breaking the cyst, pressure bandages, injection of sclerosing solution (iodine or carbolic acid), surgical excision, excision and injection of formalin or iodine, aspiration and injection of iodine or iodoform. After any of these methods recurrences may occur. Surgical excisions leave unwelcome scars; even so they are often unsuccessful because of incomplete dissection of the sac. Aspiration and injections must usually be repeated. Cherry and Ghormley[312] reviewed results, their own and others, from various types of treatment of 104 ganglia on hands or wrists of 102 patients (77 females, 25 males). From all methods good results occurred in 59 per cent of cases but best results were from complete surgical excision.

In 1940 treatment of ganglion by the injection of a proteolytic enzyme (caroid) was recommended. But this treatment in one case resulted in a "surgical tragedy," namely formation of an extensive subcutaneous abscess with widespread necrosis "partly chemical from the enzyme and partly due to the bacteria which it contained." Samples of caroid were found to be "heavily contaminated" with different bacteria. This remedy was strongly condemned by Key.[993]

Recently two ganglia were treated successfully by aspiration and injection of Searle's sylnasol [sodium salts of fatty acids from psyllium seed]; painful reactions

occurred two days thereafter but soon disappeared and the ganglia had not recurred three months later (Van Den Berg [1843]).

Juxta-articular Dercum's Disease (Adiposis Dolorosa). Features of adiposis dolorosa are obesity, weakness, nodular tender fatty tumors, neurologic changes and psychic disorders. To the 500 cases already reported was added another case, one with unusual neurologic phenomena, marked muscular atrophy and increase in subcutaneous tissues of legs, severe osteoarthritis of knees (McGavack and Klotz).

Rheumatic Purpura. Special associations between (1) purpura and "rheumatic" symptoms and (2) rheumatic disease and purpura were seen by Davis.[442, 443] It is well known that patients with various types of purpura often suffer from "rheumatic symptoms" [aching of muscles or joints presumably from small petechial hemorrhages in muscles or synovia—Ed.]. But Davis noted also that patients with various rheumatic diseases (rheumatic fever, rheumatoid arthritis, fibrositis) commonly exhibit purpura. Of 500 consecutive cases of skin purpura 47 (9.4 per cent) were in rheumatic patients; 21 had rheumatoid arthritis, nine osteoarthritis, nine fibrositis, seven rheumatic fever, one acute gout. All but three of the 47 patients were females, suggesting "an endocrine basis."

Davis also studied 88 patients with "hereditary familial purpura simplex"; 79 had purpura simplex, four Schönlein's purpura, two Schönlein-Henoch purpura, two "bruised on trivial injury," and had rheumatoid arthritis and one had pseudohemophilia. Of these 88 patients 60 (68 per cent) had or had had some rheumatic disease as follows: 23 rheumatic fever, eight rheumatoid arthritis, 15 "arthritis distinct from either rheumatoid arthritis or rheumatic fever," "others" (presumably 14) with "severe fibrositic or myalgic pains." In some of the families studied the ecchymoses were traditionally known as "rheumatism bruises."

[The term "rheumatic purpura" is commonly used by dermatologists, rarely by rheumatologists. The matter deserves the further attention of internists, rheumatologists, hematologists and pathologists.—Ed.]

Pellegrini-Stieda Syndrome; Para-articular Calcification at the Mesial Aspect of the Knee Joint. Recent studies did not determine the disputed nature of para-articular calcification at the mesial aspect of the knee joint. Pellegrini (1905) regarded the lesion as a periosteal proliferation or an osseous metaplasia of a ligament. Stieda (1908) considered that it constituted a small detached piece of bone from fracture of the medial epicondyle of the femur. The controversy continues. According to recent writers the condition represents (1) an ossifying epiperiosteal hematoma,[1083] (2) calcification of bursa between the tibial collateral ligament and the capsule superior to the medial meniscus,[207] (3) calcified tendon of the vastus medialis,[182] (4) "peritendinitis calcarea," location unspecified,[584] (5) calcific ligamentitis of the tibial collateral ligament,[1697] (6) calcified hematoma in soft tissue close to the medial condyle of femur,[19] (7) calcified hematoma in a heretofore undescribed aponeurotic membrane.[1287]

1. Pathogenesis. Acute or repeated trauma was regarded as the usual but not a necessary factor. According to Levinthal [1083] trauma causes periosteal rupture just above or at the proximal attachment of the medial ligament of the knee at the internal condyle of the femur. A hematoma burrows its way between deep muscle fascia and

above the periosteum, connecting with the cortex of bone. The hematoma becomes infiltrated with osteoblasts, and ossifies. Persistent pain is due to "pressure under the underlying structures." The supposed pathogenesis was nicely illustrated diagrammatically.

But Nachlas and Olpp who studied 20 cases clinically concluded that "the condition is not due to a fragment of bone from femur, a tear of periosteum or a calcified bursa." In one patient surgically treated the lesion was in a white fibrous membrane that seemed to invest the medial aspect of the condylar expansion of the knee. On cadavers this was identified as an "aponeurotic layer that hugged the medial aspect of the knee rather closely covering the tibial collateral ligament, the adductor tubercle and the tendon of the adductor magnus." Their 20 cases were in soldiers who despite their general youth, all had associated arthritis (generally osteoarthritis), presumably posttraumatic, and this condition was considered the chief cause of symptoms, not the para-articular ossification which seemed to result from an encapsulated hematoma.

Most writers spoke of the lesion as calcific and some reported spontaneous disappearance of the deposits (Allen [19]). But removed specimens showed bony tissue.[1083, 1287] The calcific shadow is connected to bone [1083] or may be,[19] according to some, but others [246, 584, 1287] insisted that careful roentgenography always reveals a soft tissue gap between the deposit and bone, which gap is "an essential finding in the diagnosis." [1697] In cases in which "the calcification is old, large and attached to bone, it may be confused with a neoplasm." [19] Speed noted a case in which amputation had been done because of tragic confusion with osteogenic sarcoma.

[The orthopedic colleagues of one of us, P. S. H., have studied 52 cases and concluded that the condition represents posttraumatic calcification of the medial collateral ligament. Obviously a variety of lesions have been described under the term "Pellegrini-Stieda syndrome" which is the usual fate of ill-defined conditions given eponymic designations.—Ed.]

2. Treatment. Conservative treatment for the mild pain or tenderness was generally advised. With physical therapy, deposits disappeared in two cases.[1287] Roentgen therapy was recommended.[584] Surgical excision is rarely required,[1287] but will give relief if conservative measures do not help.[1083] Treatment of the commonly associated arthritis may be more important than that of the calcific lesion.[1287]

Aseptic Necrosis of Bone. Any obliterative process which interferes with blood supply to bone may initiate aseptic necrosis. If the necrosis occurs in epiphyseal bone near a joint, secondary osteoarthritis usually results. If the necrosis occurs in the shaft, bone infarcts result. Aseptic necrosis of bone is posttraumatic or nontraumatic. The traumatic type usually affects subchondral bone in one region only, chiefly a hip. The nontraumatic type may affect subchondral bone or shaft and produce multiple or single lesions.

1. Posttraumatic Type. Chief causes of traumatic interference with blood supply to subchondral bone of femoral head were listed as fractures of femoral head, epiphyseal separation, traumatic dislocation and congenital dislocation.[130] The sequence of pathologic reactions leading to secondary osteoarthritis was outlined (Bergmann; Politzer). Contrary to common opinion aseptic necrosis of femoral head is not always due to interruption of blood supply from the ligamentum teres; in one case proved aseptic necrosis occurred after traumatic dislocation despite the presence of a normal ligament (Kleinberg). Two cases following adolescent femoral epiphysiolysis were noted.[1259]

2. Nontraumatic Types. These comprise ones of unknown cause and others related to decompression sickness. Since the aseptic necrosis related to Legg-Perthes' disease or to osteochondritis dissecans often has no apparent relationship to gross or

even to microtrauma, some writers preferred to list it as the nontraumatic variety.[130, 1396] Politzer also objected to labeling as "osteochondritis" the various necrotic lesions of growth centers since no evidence of inflammation has been found to support the suffix "itis." In such cases the end result (whether or not late disabling secondary osteoarthritis develops) depends largely on the age of the patient at the time of the initial lesion and on the site, whether or not it is a weight-bearing joint. The older the patient and the more weight the affected joint must bear the more likelihood for the development of secondary osteoarthritis.[1396] Aseptic necrosis of a semilunar bone of a child [1396] was reported for the first time.

Aseptic necrosis and bone infarcts commonly affect caisson workers subject to increased atmospheric pressures and the need for controlled decompression. Acute symptoms of faulty decompression ("decompression sickness") are "the bends"; late symptoms which concern bones or joints result from "gas embolism" chiefly nitrogen bubbles. Sites chiefly affected have been long bones and hip or shoulder (Allan). Aseptic necrosis may develop in caisson workers who have not had the "bends" (Taylor [1779, 1780]).

Aviators flying at altitudes above 30,000 feet may likewise have acute aeroembolism, one feature of which is acute pain in joints or bones, sometimes mild, sometimes "excruciating." The pain disappears on descent.[142, 1721] But no infarcts or aseptic necrosis of bone have been recorded among air personnel.[1779, 1780]

Osseous and articular lesions identical to those of caisson workers have been found in persons never subjected to abnormal atmospheric pressures or to known trauma. The cause of the aseptic necrosis in such cases is unknown but the vascular interruption has been blamed on fat emboli, bland infarcts, septic foci, peripheral vascular disease. Taylor [1779, 1780] reported 41 such cases.

Ehlers-Danlos Syndrome. Cases were presented illustrating the three chief features, friability of skin and blood vessels (dermatorrhexis), overelasticity of skin (dermatocholasis) and overelasticity of joints (arthrocholasis).[74, 118, 1491, 1743, 1778] In one case creatine metabolism was abnormal.[1393]

Osteopathia Condensans Disseminata. Two cases of this condition (osteopoikilosis: spotted bones) were reported.[60, 1285]

Osteosclerosis. Cases of osteosclerosis with anemia or nonleukemic myelosis were noted.[219, 701]

Morton's Metatarsalgia. The cause is now known to be a tumor in the fourth plantar digital nerve (a posttraumatic degenerative fibrosis of the nerve with neuromatous proliferation). Excision of the tumor relieved all 23 patients.[61, 1196, 1756]

Arachnodactyly. Findings at necropsy in a case complicated by dissecting aortic aneurysm with rupture were presented with a review of four other reported cases of arachnodactyly and heart disease in which necropsy was done.[538]

Physiology of Joints, Cartilages and Muscles

Joints. 1. Nerve Supply. The nerve supply to articular and periarticular structures was reinvestigated (Smyth and Freyberg).[608, 1650] Joints are supplied by mixed nerves which innervate also muscles, bones and skin of the same area. No nerve fibers were found in compact bone or cartilage. The nerves terminate as free nerve endings, or in a terminal plexus, or in special nerve organs. The sensory innervation of joints may not derive from the same source as that of overlying superficial areas.

2. Pain. The nature of stimuli causing joint pain was discussed (McEwen;[1198] Smyth and Freyberg [608, 1650]). Smyth and Freyberg [1650] found *predictions* of weather (not effect of weather on symptoms) by 20 "arthritic patients" wholly unreliable. [Type of arthritis not stated.—Ed.] The diagnostic indications of pain in various specific joints and the rationale of rest, drugs, local anesthesia, roentgen

irradiation, heat and splints for control of pain were presented. Freezing of skin over joints with ethyl chloride caused disappearance of pain in fractures near joints, stenosing tenosynovitis and low backache (Henry). [The evidence was not convincing. —Ed.]

3. Motion. A new hip arthrometer allows recording of a 3-dimension, graphic illustration of hip motions, also minor degrees of limitation of motion.[638] A simple useful arthrometer with a fixed horizontal indicator was used by Cooper.[372] West used an inexpensive carpenter's boxwood rule as a goniometer. Two new methods of recording joint measurements [1253, 1939] and another functional classification of joint motions [455] were described.

Synovial Tissue. Staining reactions with Southgate's mucicarmine stain and metachromic dyes gave no evidence of mucin secretion by synovial cells (Davies [436]). Metachromasia was only present in "mast" cells along blood vessels. Mitochondria, but not Golgi bodies, were demonstrable in lining cells and the underlying connective tissue cells.

The absorptive function of the synovial membrane in various joint diseases was tested by Efskind with parabrodil and indigo carmine. In hemarthrosis from slight injuries and in "hydrops" of unknown origin there was no change from normal. In "arthrosis deformans" both substances were retained (parabrodil, three to four hours; indigo carmine, 12 to 18 hours). The longest periods of retention occurred in pyarthrosis (12 hours with parabrodil, 24 hours with indigo carmine).

Following intravenous injection in calves, thiocyanate and glucose diffused readily into joint spaces (Zeller, Bywaters and Bauer). Serum and fluid thiocyanate equilibrium was usually attained in one to four hours. The concentration in the fluid averaged 9 per cent lower than that in blood; that in aqueous humor was lower than that of synovial fluid; only traces were present in cisternal fluid.

Synovial Fluid. The viscosity of synovial fluids differs in various joints of the same animal (Davies [437, 438]). Highest viscosities were found in the axial joints. No histologic differences were found in the synovial membranes to account for differences in viscosity.[437] Cell counts were higher in joints of head and neck than in those of extremities. Age and cell count were not related in cattle, but in sheep counts decreased with age. The axial joints showed relatively slight degenerative changes.[438]

In edematous persons the synovial fluid is increased in amount (Coggeshall, Bennett, Warren and Bauer). Total nucleated cell counts were often increased in fluids from patients dying from varying degrees of (primarily nonarticular) infection. An increase in the absolute neutrophil count was a more sensitive index of synovial inflammation than the total count. The marked synovial tissue reactions in patients with septicemia were of the type seen in early cases of specific infectious arthritis.

Bactericidal activity was demonstrated for streptococci in only 11 per cent of 37 synovial fluids, for *Escherichia coli* in 87 per cent of 39 fluids. The activity for *Escherichia coli* was related to the complement content of the fluid (deGara).

Intra-articular injection of testicular extract reduced the viscosity of synovial fluid in three cases of rheumatoid, and in one case of traumatic arthritis. This change apparently did not result from dilution but from hydrolysis of hyaluronic acid in vivo as the protein content remained relatively constant (Ragan and DeLamater).

That the glycolytic enzymes in synovial fluid are present almost entirely in the leukocytes was shown again (Hubbard and Porter). But two of 14 fluids showed glycolytic activity even after removal of cells. The rate of destruction of glucose added to synovial fluid was at least twice as great as that of fructose.

The "nucleoproteid" of normal joints is digested by normal urine but the urine of rheumatic patients (not defined) loses this power (Freund [600]).

Cartilage. 1. Chemistry. The solubility, stability and content of the main poly-

saccharide component, chondroitin sulfate was studied by Hass and Garthwaite.[790, 791, 792] Calcification of costal cartilage was correlated with decrease in this polysaccharide associated with aging. A histochemical reaction of unknown nature but thought to be specific for cartilage cells was described (Hass [791]).

2. Growth. Injury to the epiphyseal cartilage plate in young rats and rabbits caused partial to complete arrest of growth; excision of the epiphysis was healed by a transient cartilage which did not contribute to growth (Banks and Compere).

Cartilage from rabbits less than 24 days old, transplanted into the same or other rabbits grew. Cartilage from these young rabbits grew in adult hosts while adult cartilage failed to grow in young hosts (Dupertuis). Autogenous cartilage grafts in dogs remained viable during one and one-half years of observation. Growth was not observed, presumably because the subjects were adult (Gutman and Gutman [718]).

The process of cartilage regeneration was observed microscopically by means of transparent chambers implanted in rabbits' ears. Cartilage was formed slowly in relatively avascular regions by motile granular cells of undetermined origin (Clark and Clark).

3. Aging. The reported alterations in the articular cartilage (of mice and guinea pigs) due to hormonal and other factors are of particular interest to students of articular disease (Silberberg and Silberberg [1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615]). Hypertrophic and retrogressive changes were frequent in normal old mice, but advanced changes were relatively rare.[1609] The incidence and severity of articular cartilage lesions were increased by anterior pituitary hormone but apparently decreased by estrogen, testosterone, thyroid and parathyroid hormones. Effects noted were influenced by the age of the animal when the hormone was given.

4. Metabolism. The presence of a phosphorylase in calcifying cartilage was reported.[718, 719] This enzyme, catalyzing the formation of glucose phosphate from glycogen and inorganic phosphate, provides the substrate required by bone phosphatase. In vitro calcification was blocked by agents inhibiting the glycogenolysis except when suitable phosphoric ester substrates for phosphatase were provided.

Injections of potassium iodide into growing mice caused a transient increase in formation of bone and cartilage followed by an accelerated regression (Silberberg and Silberberg [1616]). [The exact significance of these findings is unknown.—Ed.] These effects were qualitatively similar to those following administration of thyroxin or of an anterior pituitary extract. Cell density in bovine cartilage decreases with age. The glycolytic power per cell is undiminished with age but cellular oxidative capacity is progressively reduced, according to Bowie, Rosenthal and Wagoner.[194, 1507, 1508, 1509, 1859] [The statistical evaluation of the widely scattered and overlapping data is difficult.—Ed.] This reduction in cellular oxidation was attributed to a decline in oxygen activating systems rather than to dehydrogenating mechanisms because of the finding that oxygen consumption in the presence of methylene blue was independent of age.

[The latter conclusion rests on the assumption that the dye provides an excess of activated oxygen and so leaves as limiting factors the mechanisms concerned with oxidation of substrates by removal of hydrogen. Unpublished studies by one of us, W. B., indicate that the methylene blue reaction has nothing to do with tissue respiration.—Ed.]

Muscles. Recent contributions to the physiology of muscles (169 references) were reviewed by Solandt. Earlier claims that gelatin feeding markedly increased the amount of work performed by male subjects were not supported (Karpovich and Pestrecov). The disturbed creatine metabolism present in certain neuromuscular diseases of man was not improved by the administration of vitamin E,[1238, 1559] vitamin B_6 (pyridoxine) or ascorbic acid.[1238] Vitamin E plays an

essential part in the metabolism of skeletal muscles in all species of mammals so far investigated but its importance in the nutrition of human muscle is still uncertain.

Other Studies on Joints and Related Tissues

Arthritis in Animals (Naturally Occurring). "Joint-ill" is a form of suppurative polyarthritis in young lambs, caused by alpha hemolytic streptococci, Lancefield group C. Infective endocarditis was present in animals spontaneously or experimentally infected (Blakemore, Elliott and Hart).

"White scours," a polyarthritis of young equine or bovine animals, is said to resemble rheumatoid arthritis and is thought to be due to a filtrable virus. Its early articular lesions were studied by Goldberg.[662] Earliest changes in cartilage were a surface "blister" and blood vessels budding into cartilage; in synovium, hyperemia and minute hemorrhages. Later features were synovial pannus growing over cartilage, thinning and dissolution of cartilage and its replacement by granulation tissue, villous and papillary overgrowth of synovium with perivascular infiltration of lymphocytes and plasma cells.

The spontaneously occurring suppurative arthritis of rats and mice due to pleuropneumonia-like organisms was studied further. The strains recovered by Preston [1411] appeared identical with that described by Klieneberger (1938) as "L 4." A strain of the pleuropneumonia-like group recovered from a rat spontaneously affected was identical with one recovered from rats inoculated with material from a patient with acute rheumatic fever. Admittedly the latter strain might have been of rat, rather than human, origin (Beeuwkes and Collier).

Experimental Arthritis. This can be produced by many different agents listed by Westcott.

1. Bacterial. Arthritis in rats and mice was produced by injections of various strains of pleuropneumonia-like organisms [1406, 1411, 1412] and was generally fatal.[1406] The suppurative arthritis produced resembled human pyogenic arthritis rather than rheumatoid arthritis.[1411] The arthritis in rats could be prevented [1406, 1411] or notably minimized by injections of myochrysine given with or shortly after the infective dose. Also similar arthritis in mice was cured by various gold, but not by sulfur, compounds (Preston, Block and Freyberg [1412]), penicillin (Powell and Rice [1406]), neoarsphenamine, bismuth, salicylates or sulfapyridine (Sabin and Warren [1524, 1525]).

Rabbits sensitized to products of hemolytic streptococci often developed synovial reactions after intravenous injections of homologous culture material (Angevine, Cecil and Rothbard).

Experimental hemolytic streptococcic arthritis in rats was prevented but not cured by myochrysine (Rothbard, Angevine and Cecil) but the prophylactic dose was close to the lethal dose. Purulent arthritis was produced in rabbits by intravenous injections of *Staphylococcus aureus* (Rigdon). A strain of *Streptobacillus moniliformis* from a patient with rat bite fever was used to produce infection of chick embryos; invasion of blood stream and almost exclusive localization of the infection to synovium occurred (Buddingh).

2. Hormonal. Polyarthritis was produced in adrenalectomized or thyroidectomized female albino rats by overdosage with desoxycorticosterone (Selye, Sylvester, Hall and LeBlond). The incidence of arthritis was higher if the animals were exposed to cold. The polyarthritis histologically resembled that of acute rheumatic fever and was often associated with Aschoff bodies. Selye and Pentz [1577] also reported the occurrence of rheumatic carditis, periarteritis nodosa and nephrosclerosis following the administration of large amounts of desoxycorticosterone in unilaterally nephrectomized rats. The authors concluded that the pathogenesis of rheumatoid

arthritis, rheumatic fever and periarteritis nodosa may be related to adrenal insufficiency.

[These results are as yet unconfirmed by other workers. Further studies are needed to eliminate the possibility of spontaneously occurring arthritis due to streptobacilli or pleuropneumonia organisms in the rats.—Ed.]

3. Chemical. Intra-articular injections of silver nitrate produced acute arthritis and subsequent atrophy of adjacent muscles. The atrophic muscle revealed abnormal synaptic behavior and was resistant to curarization. Prostigmine produced less potentiation and more depression in the "arthritic" than in normal muscles.[618]

Articular Roentgenography. To discover traumatic lesions of knees not demonstrable in conventional views, special views to demonstrate the intercondylar notch and certain aspects of the patella were advised.[284] Technics for improved visualization of lumbosacral junction[390] and the foot[626] were described. Widening or obscurity of the obturator shadow was valuable in early roentgenographic diagnosis of septic hip disease.[808] "Pneumoroentgenography" was advocated in cases of persistent knee disability.[161, 414, 795, 1675]

Rheumatic Diseases and the War

Influence of War on the Incidence of Rheumatic Diseases among Civilians. During wartimes in the past the *general* health of the people behind the lines has, paradoxically, improved. During World War II this was again generally true in countries which maintained their freedom. But the incidence of certain diseases did not follow the general pattern of improved health. In Great Britain the incidence of acute rheumatic fever declined notably but that of chronic rheumatism increased, presumably for the following reasons: "Many people previously employed in light work are now engaged in much heavier tasks. The housewife makes munitions; the woman factory worker does work previously performed by men. 'Digging for Victory' bringing into action muscles long disused, can be another promoting cause of rheumatic trouble if early indications are neglected. It is well recognized that in a certain proportion of cases of rheumatoid arthritis the onset of the disease follows a shock."[886]

[No actual figures on the incidence of chronic rheumatic diseases were given. —Ed.]

In Great Britain the incidence and severity of acute rheumatic fever, steadily declining before the war, fell at a "greatly accelerated" rate during the war; its death rate was halved. This wartime decline resulted presumably because of a decrease in poverty owing to abundant employment, the feeding program (milk, solid food) for school children, the "long changes of air" (country life) due to evacuation from cities, and perhaps "a change in the relationship between man and the *Streptococcus pyogenes*" (Glover).

Influence of War on the Incidence of Rheumatic Diseases among Military Personnel. Based on previous experiences a high incidence of rheumatic diseases among American[1378] and British military personnel[526a] was expected. "Apart from other conditions of service, the intensive development of mechanized warfare will make them subject to conditions known to be specifically productive of rheumatic disease in industrial life—frequent small bruising and tearing injuries, working in cramped conditions, frequent alterations of heat and cold."[526a]

To what extent this expectancy was borne out cannot yet be stated precisely since the figures on incidence are just now being compiled. But certain generalizations can be made from the data under review.

Relation of Rheumatic Diseases to War. In their relationship to war "rheumatic diseases" can be divided thus: (1) those peculiar to war and military service, (a) infected wounds of joints (septic and traumatic arthritis), (b) traumatic lesions of joints and related structures caused by noncombat trauma of a military type (long marches, mechanized warfare, paratroop injuries), (c) rheumatic diseases related to military herding (epidemic rheumatic fever; articular complications of scarlet fever, meningococcic or streptococcic infections), (d) lesions induced by excessive (military) exposure to cold and wet, (e) articular diseases arising from the location of troops in certain regions (epidemic tropical acute polyarthritis; "epidemic" coccidioidomycosis); (2) those coincidental to war and military service, (a) recurrences or exacerbations of preexisting rheumatic fever, rheumatoid arthritis, fibrositis or gout, favored perhaps by military life, (b) appearance of certain rheumatic diseases, rheumatoid arthritis, osteoarthritis, fibrositis, nonepidemic rheumatic fever, while the soldier was under no *special* military stress (in camp or not in zone of combat), (c) articular complications of venereal diseases.

Somewhat to their surprise and "disappointment" American rheumatologists who entered military service saw relatively little articular diseases specifically related to war (septic arthritis from war wounds, or rheumatic diseases specifically induced by fighting under battlefield conditions of cold and damp). The "rheumatic diseases" of World War II were of a more prosaic kind and comprised four chief conditions: epidemic rheumatic fever among military personnel in certain training areas; psychogenic rheumatism; the ever-present and ever-developing rheumatoid arthritis, particularly spondylitis, and musculoskeletal lesions related to trauma. Of much less importance statistically, though sometimes of greater academic interest, were all the other conditions encountered.

Articular Diseases Peculiar to Military Service. 1. Wounds of Joints. Early in World War I wounds of joints commonly resulted in sepsis, amputation and death, sometimes a stormy convalescence and recovery with ankylosis (Anderson [25]). Later developments in treatment improved the outlook materially, but even so wounds of joints still posed a potentially serious problem in the early years of World War II. Thus among 237 wounds of knee in the British Libyan Campaigns (1941–1942) suppurative arthritis resulted in 35 per cent; amputations were required in 4.4 per cent; death occurred in 2 per cent.[260] Fortunately the use of better technics, the availability of sulfonamides and the development of penicillin changed matters completely so that later wounds of joints often produced no significant sepsis and when septic arthritis did develop, it was handled so well in forward echelons that septic arthritis and its results became a negligible factor in general hospitals and rheumatism centers in the zones of the interior. Thus in 1944 results in 101 cases of wounds of the knees were as follows: normal knees in 75, "useful knees" in 15, stiff knees in 11; no deaths, no amputations.[260]

The general management of wounds of joints was outlined. Front-line surgery included (1) preliminary treatment of shock and sepsis, (2) "surgical toilet" of wound, (3) sulfonamide-dusting, (4) vaselin gauze without closure, (5) splinting, (6) evacuation. Later treatment at an evacuation hospital usually included arthrotomy for débridement (removal of fragments of bullet, bone and cartilage), excision of devital-

ized skin and other tissue, sometimes aspiration or irrigation of joint cavity, local and general use of sulfonamides or penicillin, closure of articular cavity as early and completely as possible, immobilization by "closed plaster" or splint. "After-treatment" included such aspirations, secondary arthrotomies, redressings, sequestrectomies and other orthopedic procedures as necessary.[25, 104, 137, 138, 140, 260, 408, 521, 621, 689, 1009, 1124, 1140, 1141, 1314, 1420, 1653, 1867, 1870] Emphasized was the value of early treatment to prevent or minimize sepsis and destruction of cartilage. "Send the surgeon up to the patient, not the patient back to the surgeon."[1141]

2. Lesions from Noncombat "Military Trauma." Internal derangements of knees resulted from training exercises, camp sports and other noncombat trauma. Results of elective surgery were disappointing and such surgery was officially discouraged except in selected cases.[1868] In such cases surgery was often followed by the patient's return to full duty.[279, 299, 1000, 1689, 1930] Special roentgenography aided in diagnosis.[284, 795, 1675] Cases of osteochondritis dissecans[286, 329] and Pellegrini-Stieda syndrome among soldiers[1287, 1697] were noted. Traumatic tenosynovitis and bursitis of feet and legs affected infantry troops[444, 916, 947]; suprapatellar tenosynovitis affected certain bomber pilots.[369] Cases of herniated nucleus pulposus were common among soldiers. In general operations were performed only for those which resulted from military service.[798, 1688] In selected cases surgical results were as satisfactory among soldiers as among civilians (Haynes[798]; Robertson and Peacher[1474]; Spurling and Thompson[1688]; Spurling and Scoville[1687]). Cervical as well as lumbar disks were affected.[1687] Medical officers assisted in the development of pantopaque myelography.[36, 117, 386, 494, 498, 647, 1555, 1678] Certain cases of "military lame back" were ascribed to faulty posture.[1795]

3. Rheumatic Fever Related to Military Herding. In the section on "Rheumatic Fever" were discussed the "epidemics" of acute rheumatic fever which affected military personnel in certain American army and navy training centers situated mostly in the "rheumatic fever belt" north of 35 degrees of latitude, especially in the Rocky Mountain and Great Lakes regions. Most affected were those in army camps in Colorado and Wyoming, naval stations at Newport and Great Lakes.[704, 856, 1132, 1174, 1176, 1919, 1969] Certain American troops on hospital ships being evacuated from tropical South Pacific regions were likewise affected.[1686] British naval recruits at certain training centers were affected.[691, 692, 693, 694, 967] Observations on rheumatic fever among British troops isolated at a remote desert camp in Burma, among troops in the Middle East (Kersley[989]), and among recruits and civilians in Malta were also made.[379, 1819]

So numerous were the cases in American camps in 1942 and 1943 that special measures were taken. The Army Ground Forces instituted researches under two special commissions.[1473] The Army Air Forces set up a rheumatic fever control program with convalescent centers in regions relatively devoid of streptococcic respiratory infections.[532, 855, 999, 1454, 1845, 1910] Research units were established by the navy.[331, 1885, 1886, 1920] Canadian medical officers also studied the problem.[547, 757] New methods of treatment were tried out by army and navy medical officers. Penicillin was found to be ineffective.[269, 578, 1432, 1884] Large doses of salicylates given intravenously were recommended,[330] but later found to be not superior to older methods of salicylate administration. Most effective was sulfonamide prophylaxis carried out extensively among army[855, 1074] and naval personnel.[294, 331] Promising results also were obtained by control of airborne infection in army camps by special care of barracks and bedding, use of aerosols and others.[1473]

Studies on the incidence of rheumatic heart disease among candidates for military service were made.[1090, 1514]

4. Other Infections Related to Herding. The relation of epidemics of scarlet fever to rheumatic fever were studied; most of the articular complications of scarlet

fever were regarded as precipitated attacks of rheumatic fever, not true scarlatinal arthritis.[1885, 1886]

Relatively minor epidemics of meningococcic infections affected American,[431, 1153, 1498, 1738] Canadian,[467] and British [375] troops. The prophylactic measures used against other air-borne infections practically eliminated these also. Articular complications of meningococcic meningitis or of meningococcemia without meningitis were fairly common and at times resembled acute rheumatic fever. Response of the articular lesions to sulfonamides was often, but not always, satisfactory. Penicillin was promptly effective in some cases,[1375] but not in others.[1498]

Small outbreaks of epidemic pleurodynia (Bornholm disease) affected American,[1192] British,[1926] and New Zealand [12] military personnel.

5. Articular Diseases Encountered in Special Localities. Epidemic acute tropical polyarthritis, a "new" rheumatic disease, was discovered among Australian and American troops in the Northern Territory of Australia and on adjacent islands. As noted elsewhere, its recognition and description were entirely the work of medical officers. The excellent character of these studies does credit to those concerned and shows that original work can be done by alert medical officers even in the field with meager laboratory facilities.[742, 775, 841, 1270, 1605]

The articular complications of acute primary coccidioidomycosis ("desert rheumatism") often escape precise diagnosis. Coccidioidomycosis is chiefly endemic in the San Joaquin Valley of Southern California. During the war, troops were concentrated for training in certain areas not known to be infected. A small number of cases (about 200 reported) of acute, and some (about 55 reported) of chronic (granulomatous), coccidioidomycosis resulted.[460, 671, 672, 1190, 1595, 1925] The military implications having been appreciated, a control program was set up.[460]

Rheumatic Diseases Coincidental to War and Military Service. 1. General. Studies on the total and relative incidence of rheumatic diseases among American and British troops indicated that the overwhelming majority were cases coincidental to, rather than resultant from, military service. Among armies (as among civil populations) totaling several million men, thousands of cases of acute or chronic rheumatism were bound to develop regardless of war. "Recruits are generally healthy people, but a certain number will have inherited a rheumatic diathesis and be liable to develop rheumatism especially after exposure or strain." [1298] Military service undoubtedly provided certain predisposing or aggravating factors (which sometimes operated earlier or more potently than might have occurred otherwise) but most of the rheumatic diseases encountered would have developed whether their victims were in "civies" or in uniform.

In World War I "chronic arthritis" (presumably mostly rheumatoid type), rheumatic fever, muscular rheumatism and gonorrheal arthritis (in the order named) comprised the bulk of rheumatic diseases among American troops.[816, 817] In World War II American troops were chiefly affected by muscular rheumatism, "tenosynovitis or synovitis," rheumatoid arthritis and rheumatic fever. Much of the muscular rheumatism, tenosynovitis and rheumatic fever cleared up. Those rheumatic soldiers who did not improve but were sent to the army's five rheumatism centers generally had rheumatoid arthritis, psychogenic rheumatism, residues of rheumatic fever, or chronic muscular or capsular rheumatism (fibrositis).[173, 176, 816] Compared to American experiences the diagnosis of "fibrositis" was made four to five times as often among British troops; the reported incidence of rheumatoid arthritis was less than half that among American troops and "psychogenic rheumatism" was either rarely encountered or rarely recognized or diagnosed as such.[890, 989, 1541]

[These differences probably represent differences in diagnostic criteria and standards. —Ed.]

2. Miscellaneous Observations. Among rheumatoid soldiers the ratio of spondylitis to arthritis of peripheral joints was unusually high—1:3 or 1:2 as compared to the proportion of 1:6 or 1:13 among civilians.[173, 176, 816, 1408, 1599] Although few in number, most of the recently reported cases of Reiter's syndrome were among soldiers.[637, 858, 1504, 1599]

As already stated American soldiers with "psychogenic rheumatism" provided a real problem on the "psychiatric" and "rheumatism services" of general hospitals and at the army's rheumatism centers.[144, 174, 581, 631, 748, 816, 1531, 1544, 1905] Such cases comprised 15 to 20 per cent of "rheumatic cases" at rheumatism centers.[816] Only one Canadian [802] and two British reports [524, 571] have been noted.

Despite an increased incidence of gonorrhea among military personnel, the incidence of gonorrheal arthritis, thanks to chemotherapy, fell remarkably, to as low as 0.1 or 0.3 per cent.[1826] In most of the few reported cases prompt cure occurred if enough penicillin was given.[413, 754, 815, 816, 928, 1790] The supposed "gonorrheal arthritis resistant to penicillin" seen at one rheumatism center appeared in most cases to be rheumatoid arthritis precipitated, reactivated or notably aggravated by acute genital (not articular) gonorrhea.[816]

The studies in the following list made by medical officers or others, pertaining to articular or rheumatic conditions among soldiers, have been referred to in the appropriate parts of this Review: unusual articular diseases (palindromic rheumatism) [1793]; articular symptoms of periarteritis nodosa [1183, 1184]; of decompression sickness [1721]; dermatomyositis [1617]; psoriatic arthritis [589]; tumors of joints,[109, 329] tabetic neuroarthropathy,[1960] articular reactions to penicillin [the first reported case [681] —Ed.], or to sulfonamides [1153]; certain clinical investigations [63, 175, 377, 382, 384, 548]; miscellaneous reports.[573, 853, 1099, 1127, 1343, 1991]

The Campaign against Rheumatism

In every country surveyed the same findings have been made: (1) rheumatic diseases outranked all others as a cause of chronic morbidity; (2) rheumatic diseases annually involve each country in great expense; (3) adequate facilities for the care of most rheumatic patients are nonexistent. In the United States as elsewhere the total army of rheumatic victims is relatively neglected. Compare their prospects with that of others, for example, the tuberculous: for our 680,000 tuberculous patients there are available about 100,000 free beds and $100,000,000 for care and research. But for our 6,850,000 rheumatic patients there are available only about 200 free beds and $200,000 for care and research. In other words although there are 10 times as many rheumatic as tuberculous patients the latter have available 500 times more beds and money. Thus the tuberculous patient, happily thereby a "vanishing race," receives 5,000 times as much attention as the nonvanishing rheumatic.

A recent survey of American voluntary health agencies (Buell [250]; Dublin [485]; Gunn and Platt [716]) disclosed an astonishing paradox: "The greater the need the less the public's support." But as it concerns the menace of rheumatism, this is true only because the American public has not been sufficiently informed or aroused. Once enlisted, public opinion has given generous support as shown by data in table 4. Physicians concerned with rheumatic diseases, only want more financial support for these patients, not less for others.

The same situation prevails elsewhere. In England and Wales before the war there were 30,000 beds for tuberculous patients, only 1,000 for the rheumatic (Ellman [523]). Yet "rheumatism" costs the people of England and Wales over

TABLE IV

Disease Prevalence versus Voluntary Public Support

Disease	Support	Amount Collected *Annually*	Patients	Dollars Available per Patient
Infantile paralysis	Sold to public	*$16,600,000	175,000 crippled	94.00
Tuberculosis	Sold to public	15,000,000	680,000	22.00
Cancer	Partly sold to public	4,000,000	500,000 under treatment	8.00
Diabetes	Not sold to public	30,000	660,000	.05
Heart disease	Not sold to public	100,000	3,700,000	.03
Rheumatism and arthritis	Not sold to public	?	6,850,000	?

For tuberculous patients: 100,000 free beds; $100,000,000 available for care and research.
For rheumatic patients: 200 free beds; $200,000 available for care and research.
"The greater the need the less the public's support."

25 million pounds annually,[864, 865, 866] and constitutes "the greatest single enemy of social well being and economic efficiency in Great Britain."[526b] From Scotland the Medical Advisory Committee[1215] reported that rheumatism, especially the muscular type, constituted "a major health problem in Scottish industrial life" and caused more days of incapacity than any other group of diseases. In Sweden where most workers are insured, rheumatic cripples become pensionable and were doing so at the rate of 5,000 each year. Although treatment facilities there are reportedly the best in Europe, "the great majority [of patients] are not well looked after" (Copeman[381]; Sundelin).

The war interfered with notably, where it did not stop entirely, the campaign against rheumatism. But the activities of the American Rheumatism Association and the British Empire Rheumatism Council, though seriously curtailed, were continued in part. In lieu of national meetings, prevented by transportation and other difficulties, sectional programs were held by local affiliates of the American Rheumatism Association. New local groups have been formed and there are now rheumatism societies in such cities as New York, Philadelphia, Chicago, Washington, D. C. The membership of the American Rheumatism Association is now more than 400. Prior to 1910 there were no special rheumatism clinics in the United States; now there are scores, 27 in New York City alone (Snyder and Traeger[1663]). Each year several universities and the American College of Physicians have sponsored short postgraduate "refresher courses" on rheumatic diseases. During the war many American physicians with a special interest in rheumatic diseases entered military service; the military authorities wisely took advantage of their special interest and were able to assign most of them to appropriate duties so that certain clinical studies were continued. In the United States the local groups are coördinating their fund-raising efforts with those of the American Rheumatism Association to the end that plans for a unified national campaign have been made.

The Canadian Rheumatism Association was formed in 1936; a number of its members belong also to the American Rheumatism Association and the two organizations enjoy a most cordial relationship. Several Central and South American countries have flourishing rheumatism associations, notably Argentina,

Brazil and Mexico. To correlate their efforts and interest, the Pan-American League against Rheumatism was recently formed (Pemberton [1363]; Swaim [1753]).

In Great Britain despite great difficulties the activities of the Empire Rheumatism Council were continued under the vigorous leadership of Lord Horder.[526] By him and his colleagues much was accomplished as is well shown in the Council's stimulating annual reports.[526] The Council's long-range objective is to see to it that all rheumatic patients shall have available treatment appropriate to their needs. The Council has the Government's assurance that rheumatic patients will be fully provided for in its developing scheme for social medicine. Most of the funds required for this exceedingly ambitious program will come from Government. A "blue-print for national action" against the "social plague of rheumatism," prepared by Horder,[864] has been well received as a basis for discussion, "to bring the issue into the region of practical medical politics." [865] It involves eventual plans for the establishment of Regional Centers for Special Treatment and more numerous local centers, and immediate plans for post-graduate courses on rheumatic diseases, of lengths from one to several months. A prospective syllabus for such a course was drawn up (Abrahams [4]). The Council's survey of the value of current remedies led to the conclusion that thereby about 60 per cent of rheumatic patients "get a cure or substantial relief if given the right treatment at an early stage and this without serious disturbance of their industrial or domestic life." [526c] The Council subsidized 20 research projects, a chief one being a study on the causes of the high incidence of rheumatic fever in training establishments of the Royal Navy. While fostering national action the Council meantime has encouraged the establishment of new treatment centers in civic, university and industrial hospitals. Its publication, the *Annals of Rheumatic Diseases,* survived the war as the only European journal dealing specifically with the problem of rheumatism; it is now published quarterly as a supplement to the *British Medical Journal.* Using to date only private funds, the Council expended about $250,000 thus: for research 38 per cent, for treatment 36, for educational propaganda 15, for administration 11. As part of its program the Council investigated the value of 256 bona fide therapeutic suggestions sent from all over the world; but it refrained from such studies as the investigation of a certain species of apple (grown by the correspondent) which was "an infallible cure for all forms of rheumatism"! Above all the Council has effectively aroused British public opinion, "the controlling force of official action." By joining forces with the British Orthopaedic Association the Council has ensured a united front of medical rheumatologists and orthopedists on problems affecting the rheumatic patient.

In Scotland [435, 1215] and in Sweden [381] somewhat similar plans for governmental action have been drawn up. The Scottish plan recommended that the central units should not be isolated rheumatism centers but should be part of large teaching general hospitals. In Sweden certain beds in county general hospitals are to be devoted exclusively to rheumatic patients.

The Ligue Internationale contre le Rheumatisme, dormant during the war, has been revived under the leadership of Drs. Ralph Pemberton (its President), Van Breemen and others, and will hold its first postwar international congress in the United States in June, 1949.

It is interesting to compare the American and British campaigns. In this

country the emphasis has been on the improvement of voluntary community effort to be directed and unified in part by a national, but nongovernment, agency (currently the American Rheumatism Association). Thus chief reliance is placed on the contributions of individual physicians or small groups in the field of treatment and research. These "cells," working "from the bottom," often have been made up of individual members of the American Rheumatism Association who are thus making their all-important personal contribution to the national effort. But in Great Britain greater emphasis is on national action, the Government to be chiefly responsible for the financial support and organization of effort. Excepting the Heberden Society, composed largely of London rheumatologists, there is no British Rheumatism Association, no unification of the British medical profession interested in the problem. In its place the small potent Empire Rheumatism Council is the motivating force "from the top." Both campaigns are far from their goal. The weaknesses of voluntary effort are glaringly apparent [250, 485]; the potential weaknesses of governmental action and "socialized medicine" have been pointed out but cannot be fully defined until action has occurred. Each group of campaigners can learn much from the other. Contrary to the usual adage it might be well for each country to "light the candle at both ends." Thus the United States should step up its national campaign to arouse public opinion, first for strong community effort, later as necessary for supplementary governmental support consistent with the American desire. Thus Great Britain, having achieved its government's commitment for (future) national action, might well establish a British Rheumatism Association to be the main force by which national action is applied to the individual.

Regardless of details the international campaign is proceeding and is succeeding modestly. To "rheumatology" more and more physicians are devoting much or all of their time. But for full success the public must support these physicians. It is not correct to say that the public gets only what it wants or deserves and that if the public really wanted a cure for rheumatism or cancer it could obtain it by adequate support. Even with the latter the public could hardly "buy" the remedy in a year or a decade. But unfortunately much of the rheumatic public ignores the useful remedies now available. Individual initiative being what it is, the public has largely received benefits it did not request. It did not ask for the telephone, automobile or radio. But for good or ill it got them. Thus national action is largely of value as it enhances the opportunities of the individual worker and utilizes his contributions. To that all important end united effort must be obtained.

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CASE REPORTS

ACUTE THROMBOCYTOPENIC PURPURA DUE TO NEOARSPHENAMINE: REPORT OF A CASE WITH EXAMINATION OF THE MARROW *

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ACUTE thrombocytopenic purpura is a well known complication of the arsenical treatment of syphilis. Although occurring rather rarely, it is the most common of the blood dyscrasias arising from the use of the arsphenamines, and it has been seen at least once in most clinics where sizeable numbers of luetics are treated. The disorder usually occurs after a number of doses of the drug have been given, although it may follow the first injection. It is characteristically acute in onset, and often is preceded by a nitritoid type of reaction immediately after injection. The platelets may entirely disappear from the peripheral circulation, but usually begin to reappear within 24 to 48 hours, and return to normal levels within four to seven days. Recovery is the rule unless there is the complication of agranulocytosis or aplastic anemia.

Much has been written concerning the mechanism of production of thrombocytopenia. It is well known, of course, that in agranulocytosis and aplastic anemia due to the arsphenamines there is depression of the bone marrow. Some writers have logically assumed that in thrombocytopenia there is likewise a selective injury to the megakaryocytes in the marrow.[1] It is more commonly believed, however, that the platelets are destroyed in the peripheral circulation,[2,3] or are pooled in dilated capillaries.[4-8] It is apparently felt that the short course of the disease and the prompt reappearance of platelets in the blood speak strongly against the possibility of marrow injury.[9]

It is surprising, considering the apparent conviction with which such views are stated, to find in the literature only three brief references to actual examination of the bone marrow during the course of the disease. Falconer, Epstein and Wever [4] describe the marrow of a single case as follows: "A few megakaryocytes were observed on the film, but in a differential count of 500 cells none were found. Both the erythroid and the myeloid elements of the marrow apparently had been stimulated." The differential count of the marrow is not included in their report, and nothing is said regarding the morphology of the megakaryocytes. They apparently did not consider the decrease of these cells significant.

Gorrie [10] reported the marrow of a single case as showing the "picture of blood regeneration." The differential count on his case was fairly normal, but he made no mention of the number or morphology of the megakaryocytes.

The most complete report is that of Schwartz and Vander Heide [8] who describe the marrow of their case as "entirely normal; the megakaryocytes pres-

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ent appeared of normal structure, staining quality and number." The specimen in this case was obtained on the ninth day of the disease, however, well after recovery had started. It is questionable whether it represents the picture during the height of the disease.

It is evident, then, that until there have been more adequate marrow studies, it will remain impossible to say with assurance whether there is marrow injury in this disorder or not. It is in an effort to begin to answer that question that the present case is reported, with observations on the sternal marrow.

Case Report

K. J., 18 year old Negress, came to the Stanford syphilis clinic on August 20, 1943 for treatment of her latent syphilis which had been discovered on a routine Wassermann examination.

Her father had died of paresis six years before, but her blood, and that of her mother and brother, had been negative at that time. She knew of no primary lesion, but had been treated for several months for a pelvic discharge. There was no history of bleeding tendency. Physical examination at the start of treatment was negative except for hypertrophied tonsils. The bleeding time was normal (3 minutes by Duke method).

Anti-syphilitic therapy consisted of two courses of 10 weekly intravenous doses of neoarsphenamine, each of 0.45 gm., alternating with two courses of intramuscular Sobisminol, each comprising 20 doses of 0.03 gm. The Wassermann test reverted to negative, and the only untoward reaction from the treatment, about which she said nothing at the time, consisted of brief spells of headache and diarrhea following the last few doses of neoarsphenamine.

The third course of neoarsphenamine was started on January 16, 1945 without reaction. The second dose on January 30, however, was immediately followed by a rather severe bout of coughing, sub-sternal distress, nausea, vomiting and chills. She returned home, where vomiting was followed by diarrhea. Twelve hours after the injection, moderately profuse epistaxis began, accompanied by oozing of blood from the gums and small reddish spots on the lips, face and extremities. She entered Stanford University Hospital 36 hours later for study, although by the time of entry she had already begun to feel better, and the bleeding had stopped.

Physical examination on entry showed a fairly robust mulatto girl with a few fading purplish petechiae over her face, thighs and legs. There was a small subconjunctival hemorrhage on the left, but the eyes were otherwise negative and the ocular fundi were clear. There was fresh clotted blood in the nares and posterior pharynx, and oozing from the gingival margins. There were hemorrhagic spots on the lips and petechiae scattered over the palate. The tonsils were large and ulcerated. A few firm, non-tender sub-mandibular lymph nodes were palpable bilaterally, but there was no other glandular enlargement. The heart and lungs were clear. The spleen and liver were not palpable, and there was no abdominal tenderness. The extremities were negative except for petechiae. The reflexes were in order.

Blood count on entry showed severe thrombocytopenia and a rather marked shift toward immaturity in the granulocytes (table 1). There was no anemia, and no primitive cells were found. Clotting time was normal (3½ min. by Lee-White method) but bleeding time was much prolonged (21 min. by Duke method) and clot retraction was very poor. The tourniquet test produced a heavy sprinkling of petechiae. Urine and stool contained no blood.

Sternal puncture the next day (February 2, 1945) yielded a cellular marrow (table 2) which was abnormal in two respects: (1) There was a complete absence

TABLE I

Case K. J., Blood Counts

	2-1-45	2-2	2-4	2-5	2-6	2-8	2-21
Erythrocytes	4.25 M	4.71			4.12	4.06	4.43
Hemoglobin, gm. %	13.6	15.0	14.4			13.8	
Leukocytes	10,100	10,400	10,200	10,500		15,400	13,500
Neutrophiles	76%	37%	28	50		72	47
Segmented	38	28	20	42		58	43
Banded	30	9	6	8		14	4
Myelocytes	8	—	2	—		—	—
Eosinophiles	—	1	—	—		—	5
Basophiles	1	—	—	—		2	1
Lymphocytes	22	59	70	48		25	46
Monocytes	1	2	2	2		1	1
Platelets	42,000	28,000	20,000		58,000	191,000	248,000
Bleeding time		21 min.				2½ min.	

of megakaryocytes and of platelets, but a marked increase in megakaryoblasts, many of them showing signs of degeneration; (2) there was a moderate shift toward immaturity in the granulocytes, with very few segmented neutrophiles, and an increase in early myelocytes and myeloblasts. The erythroid series appeared entirely normal.

The fact that recovery was extremely likely was recognized, but in view of the persistence of the thrombocytopenia, an increasing neutropenia, and the rather alarming myelogram, it was decided to use BAL, the new arsenic antidote which had recently been made available. Consequently, on the fifth day of the disease, she was given four doses of 0.225 gm. intramuscularly in peanut oil at four hour intervals, and subsequently 0.150 gm. daily for four days. These injections were tolerated without any untoward reaction except for a few minutes after the second, when a "prickly" sensation spread from her face to the rest of her body, accompanied by a feeling of "shakiness" and anorexia, all clearing within an hour.

Clinical improvement continued from the time of entry, with prompt and complete disappearance of petechiae and bleeding tendency. The menstrual flow, which appeared on the sixth day, was of normal amount and duration. The neutropenia had disappeared by the seventh day after the onset of symptoms, and the thrombocytopenia by the tenth day. A second sternal puncture on the eighth day (February 6, 1945) yielded a marrow which differed from the first in the following respects: (1) Megakaryocytes had reappeared in considerable numbers, and while some were

TABLE II

Case K. J., Differential Counts of Sternal Marrow

	2-2-45	2-6-45
Total granulocytes	72	71
Neutrophiles	63	67
Segmented	7	12
Banded	27	32
Myelocytes	29	23
Eosinophiles	4	2
Basophiles	1	—
Myeloblasts	4	2
Lymphocytes	13	10
Monocytes	1	1
Plasma cells	1	1
Nucleated red cells	13	17
Myeloid/erythroid ratio	5.6	4.2

of the immature types, signs of degeneration had disappeared and many were actively producing platelets; (2) there was a definite shift back toward maturity in the granulocytes.

She was discharged on the twelfth day after the onset of symptoms, apparently well. A blood count on the twenty-third day was essentially normal and there has been no return of bleeding in the 20 months that she has been followed since. Antisyphilitic therapy was subsequently completed with a third course of intramuscular Sobisminol, and she was put on probation, her syphilis apparently arrested.

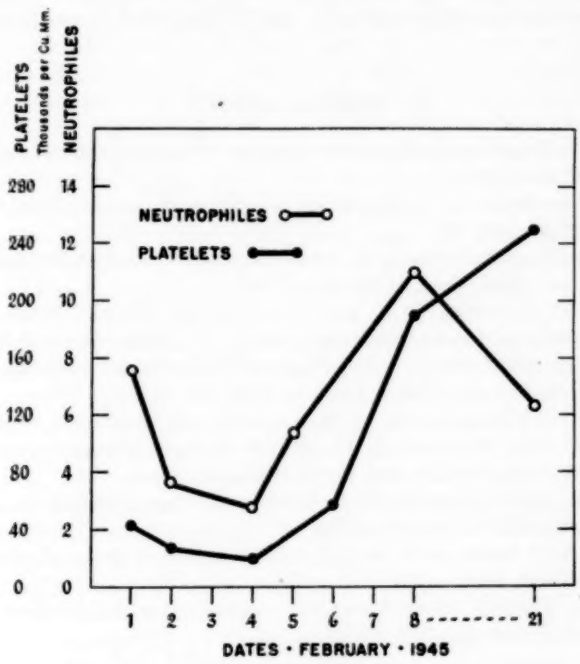

FIG. 1. Neutrophile and platelet counts. Case K. J.

DISCUSSION

This is a fairly typical case of acute thrombocytopenia following neoarsphenamine therapy of syphilis. It is characteristic in that it appeared late in the course of treatment, was ushered in by a nitritoid reaction, and was of sudden onset and short duration. As not infrequently occurs, there was a moderate neutropenia during the height of the thrombocytopenia, with absolute lymphocytosis. The bone marrow at this time showed definite evidence of damage, with destruction of the megakaryocytes and toxic changes in the megakaryoblasts, as well as stimulation of the myeloid series. These signs of damage had largely disappeared by the time of the second puncture four days later. The promptness of recovery is evidence of the transient nature of the toxic effect, and presumably dependent upon the ability of the stem cells of the marrow to produce new, active megakaryocytes. Whether the BAL contributed in any way to the favorable course it is impossible to say, as recovery is usually prompt without treatment.

No generalizations should be attempted on the basis of a single case, but it is evident that in this instance at least, peripheral destruction of the platelets or their pooling in dilated capillaries was not solely responsible for the thrombocytopenia, there being injury to the megakaryocytes as well.

Summary

A case of acute thrombocytopenic purpura due to neoarsphenamine toxicity is reported, with examination of the marrow. It is concluded that the thrombocytopenia in this case was due at least in part to destruction of the megakaryocytes in the marrow.

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HYPERTHERMIA CAUSED BY PENICILLIN-HEPARIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS *

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Since the advent of penicillin the literature contains numerous reports of cases and series of cases of subacute bacterial endocarditis successfully treated with penicillin alone or in combination with heparin. Many deleterious and even fatal results with heparin or heparin in combination with penicillin are on record. To these we wish to add a case report of excessive hyperthermia resulting from the administration of continuous intravenous penicillin to which

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From Wesley Memorial Hospital, Northwestern University Medical School.

a minimum amount of heparin had been added in order to obviate the frequent plugging of the intravenous needle. Rapidly accumulating evidence indicates that the use of heparin for any other reason in the treatment of this disease is useless, in fact contraindicated.

Case Report

G. M., a 32 year old white male, was admitted to Wesley Memorial Hospital May 31, 1946. He had been perfectly well until January at which time he complained of malaise and developed a low grade fever. A migrating type of arthritis appeared which was accompanied by subcutaneous nodules on the dorsum of his hands and feet. A physician made the diagnosis of rheumatic fever. The arthralgia, subcutaneous nodules and fever spontaneously subsided in about three to four weeks. He felt weak, had lost 20 pounds during this episode, and did not regain his usual health. About the first of May the low grade fever reappeared. He was admitted to a hospital on May 20, because of a temperature of 104° F. plus the appearance of a tender nodule in the pulp of the thumb. Blood cultures revealed alpha hemolytic streptococci. Penicillin was started and arrangements were made for him to be transferred to Wesley Memorial Hospital. About 18 hours after the first penicillin had been given and before he came to Wesley Hospital, he awakened with a severe headache and was unable to move the left side of his body.

The past history revealed an illness diagnosed as lupus erythematosis at the age of 15 for which he was treated over a period of three years with gold therapy.

Physical Examination. A poorly nourished white male lying quietly in bed exhibiting a flushed facies, apathetic attitude and appearing acutely ill. He was slightly confused and a left facial palsy was observed. Temperature 101.4°, pulse 104, respirations 20. The head was normal. The pupils and fundi were normal. No petechiae were observed in and about the eyes or on the skin. The teeth were carious and the gums were retracted and inflamed. The neck was supple. There were a few small glands in the posterior triangles of the neck. The left chest did not expand well on deep inspiration nor did the left diaphragm move well. Otherwise the lungs were normal. The heart was enlarged slightly to the right and left, there was a diffuse apex impulse with a slight anterior thrust to the chest wall. A questionable thrill was palpable. Auscultation revealed an accentuated apical first heart sound with a loud rough systolic murmur heard throughout systole accompanied by soft mid-diastolic and presystolic murmurs. P_2 was greater than A_2. The blood pressure was 118 mm. of mercury systolic and 70 diastolic. The abdomen revealed no tenderness or rigidity. The tip of the spleen was palpable and slightly tender. The liver and kidneys were not felt. The genitalia were normal. Rectal examination was normal. Tender nodules were felt in the web between the left thumb and index finger and in the pulp of the distal phalanx of the right thumb. The left arm and leg were flaccid. There was a paresis of the left side of the face except the frontalis. The tongue protruded to the left. The deep reflexes were slightly increased and there was a positive ankle clonus and Babinski on the left. Sensation was intact.

Laboratory. The urine contained a trace of albumin and a few erythrocytes. The blood count was 4 million erythrocytes, 12.5 gm. hemoglobin, 6300 leukocytes, with a differential count of 85 per cent neutrophiles, 9 per cent lymphocytes and 6 per cent monocytes. The sedimentation rate was 44 mm. per hour (micro method). A nose and throat culture showed a few staphylococci (*albus*) in the nose and many *E. coli* in the throat. Repeated blood cultures with penicillinase were negative. The prothrombin activity was 100 per cent of normal. The blood Kahn was 3 plus while the Wassermann test was negative.

Hospital Course (figure 1). In view of the recent cerebral accident (assumed to be an embolus) and the diagnosis of subacute bacterial endocarditis at the previous hospital with the recovery of the *alpha* hemolytic streptococcus and in view of the fact that the patient had received 2 million units of penicillin during the 48 hours preceding admission it was considered unwise to discontinue penicillin until we had secured positive blood cultures and reëstablished the diagnosis. Hence 1.5 million units of penicillin were dissolved in 1000 c.c. of 5 per cent glucose in distilled water and given daily by continuous intravenous drip. From the first to the eighth hospital day that dosage was maintained. By the fourth hospital day the temperature and pulse had returned to normal and remained there. On the ninth to eleventh hospital days the penicillin was reduced to 1 million units daily. Because of the difficulty experienced with the needle clogging and the scarcity of veins, on the twelfth and thirteenth hospital days the patient received 100 thousand units of penicillin intra-

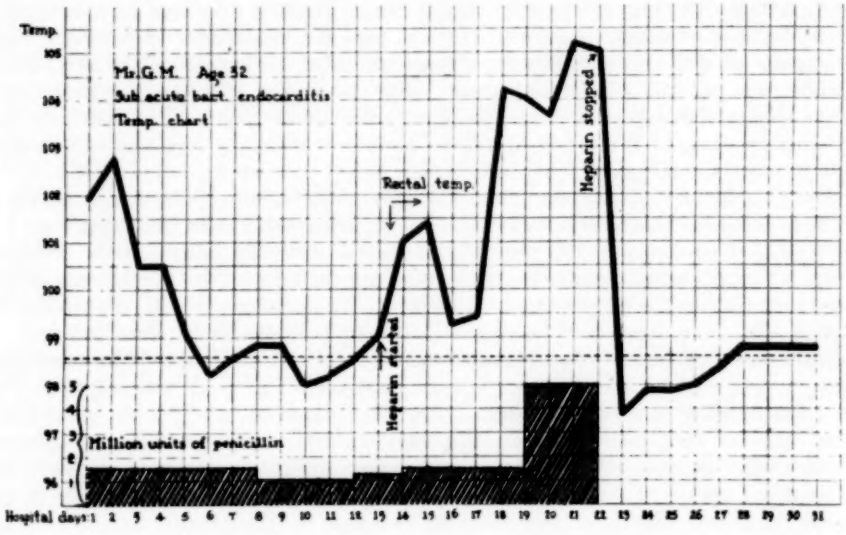

FIG. 1. Febrile course and therapy in hospital.

muscularly every two hours. Due to the patient's complaint of pain at the site of injections, penicillin was resumed by continuous intravenous drip but to each 1000 c.c. was added 20 mg. of sodium heparin to eliminate the trouble with the needle. Inasmuch as the temperature rose to 101° F. on that day and 101.4° the following day, on the sixteenth to eighteenth hospital days the penicillin dosage was increased again to 1.5 million units.

In spite of the increased dosage of penicillin, the absence of positive blood cultures, and no clinical evidence of fresh emboli the temperature gradually rose to 104.2° F. The dosage of penicillin was increased on the nineteenth hospital day to five million units and was thus maintained on the twentieth, twenty-first and twenty-second hospital days. The temperature remained between 104° and 105.2° F., occasionally falling to normal to be followed by a chill and an elevation again. The patient became clinically worse, evidence of beginning decompensation appeared, the blood non-protein nitrogen rose to 52 mg. per cent, the CO_2 combining power fell to 30 volumes per cent and the patient became gradually comatose.

By the evening of the twenty-second hospital day it appeared that unless a radical

change occurred this patient would not survive the night and since febrile reactions from heparin up to 108° F. with mental disturbances had been reported by Levy and McKrill [1] it was decided to discontinue medication. By 10 p.m. the temperature had fallen to 96° F. rectally. The patient appeared clinically improved. Orientation returned within 24 hours but the rectal temperature remained subnormal for nine days following discontinuance of therapy.

The temperature, pulse rate and blood cultures have remained normal since that time although the sedimentation rate has remained elevated. On the sixty-seventh hospital day an infected molar was removed along with the simultaneous administration of penicillin for 24 hours without untoward results. On the seventieth hospital day two additional molars were extracted while the patient was receiving a continuous intravenous infusion of penicillin and heparin for 24 hours with no reaction. On the seventy-sixth hospital day two remaining infected molars were removed accompanied by penicillin for 24 hours without incident. The patient was discharged on the seventy-ninth hospital day clinically cured although he still had an elevated sedimentation rate. He was able to walk with a circumducted gait. The paresis of the face had improved although the left arm remained useless.*

Discussion

Cultures of the alpha hemolytic streptococci were obtained from the previous hospital and titrated against various antibiotics and found to be extremely resistant in vitro by the Heilman plate method [2] requiring 6 units of penicillin or 8 units of streptomycin per c.c. to inhibit growth. Sulfadiazine did not inhibit growth up to 25 mg. per cent concentration. Penicillin assays revealed that the blood levels in our case varied between 0.5 and 2.0 units per c.c. and were consistent with those reported by Dawson and Hunter [3] and Avery, Mayer and Nelson [4] for similar dosage. The sodium heparin in the dosage used did not affect the coagulation time of the blood as measured by the Lee and White method. No sodium paraaminohippurate was available to try renal blockade of penicillin [5, 6] and we hesitated to use diodrast [7] in the dosage required, hence the increase to 5 million units per day on the nineteenth hospital day. In spite of or because of increased medication the patient's condition became worse—his fever persisted and he appeared moribund. Within four hours from the time the medication was stopped the temperature had fallen to subnormal and the patient was clinically improved although still critically ill. For nine days the temperature remained subnormal gradually approaching the base line as his clinical condition improved.

Whether the hyperthermia was on the basis of penicillin, heparin, or a combination of the two, or whether pyrogens were liberated from the rubber tubing was undetermined. However, there was no fever for several days while the patient was receiving penicillin prior to the addition of heparin to the solution. No chemical thrombophlebitis or phlebothrombosis was encountered due to the continuous intravenous infusion, although occasionally the needle had to be started at a different site because of mild inflammation along the course of the vein.

Penicillin was used at the time of tooth extractions both alone and in combination with heparin in a similar manner to its administration during the course of the illness without untoward effect. We felt justified in this course of action

* At the time this report was proof read, January 6, 1948, approximately 17 months after discharge from the hospital there had been no recurrence of the endocarditis.

both as a precautionary measure against the transient bacteremia [8] and also to try to establish the cause of the fever during the therapy. The same penicillin was used throughout, but unfortunately a different lot number of heparin was employed for the extractions.

We feel that this case should be added to those unusual reactions occurring during therapy of a disease which makes it extremely difficult to determine whether the unfavorable reaction of the patient is due to the disease process or to the medication.

Summary

A case of subacute bacterial endocarditis with recovery is reported. Prolonged hyperthermia of alarming degree accompanied the use of large amounts of penicillin with minimal amounts of heparin. The evidence points toward heparin as the cause of the hyperthermia.

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EDITORIAL

THE PRESENT STATUS OF FOLIC ACID IN THE THERAPY OF MACROCYTIC ANEMIA

THE control of Addisonian pernicious anemia by the use of liver undoubtedly represents one of the most notable contributions of modern medicine to the welfare of mankind. Castle's hypothesis,[1] conceived as a result of a series of ingenious clinical investigations, supplied the theoretical basis for an understanding of the mode of development of this and related macrocytic anemias. The effectiveness of extracts of liver in a variety of clinical entities has usually been explained by reference to this "unitarian" hypothesis which was based upon the interaction of an "extrinsic" dietary factor with an "intrinsic" gastric factor leading to the formation of the anti-pernicious anemia principle subsequently absorbed through the intestinal wall and stored in the liver. Critical investigations carried out in an effort to challenge the hypothesis have usually been unsuccessful. Nevertheless, in the case of certain well-defined entities, for example, tropical macrocytic anemia and "pernicious" anemia of pregnancy, characterized not only by peripheral macrocytosis but by distinct megaloblastic hyperplasia of the marrow, application of the hypothesis has not been entirely successful. Cases of this variety have frequently demonstrated refractoriness to parenteral treatment with a highly concentrated liver extract while subsequently improving upon the oral administration of crude liver extracts or autolyzed yeast preparations.[2] Some factor other than the anti-pernicious anemia principle seemed to be the effective therapeutic agent and Castle and Watson [3] proposed the use of the term "Will's Factor," named for Lucy Wills, a pioneer in the investigation of these anemias.

There has been no definite way hitherto of determining whether a single substance in liver extract was responsible for the improvement observed in the varied pathological manifestations of pernicious anemia. It has been long suspected, however, that multiple deficiencies existed in this disease. The chemical structure of the factors concerned in the Castle hypothesis has not been determined. The occurrence of the extrinsic factor in many foods which are a rich source of the vitamin B complex led early to consideration of a possible relationship. However, with the isolation and synthesis of each new member of the complex its ineffectiveness in the treatment of pernicious anemia was established.[4]

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The recent isolation and synthesis of "folic" acid has for the first time furnished a pure substance which could apparently produce a hematologic and clinical remission in Addisonian anemia. Folic acid was found to be equally effective whether given parenterally or orally. Its effectiveness on oral administration immediately challenged its identification with extrinsic factor. Further difficulty was encountered when identification with the anti-pernicious anemia principle of concentrated liver extract was attempted. It was found [5] that commercial liver extracts highly effective in treatment contained only infinitesimal quantities of folic acid, far below the therapeutic requirement for the pure vitamin. The relationship of folic acid to the factors concerned in the Castle hypothesis is interesting to examine in more detail.

The isolation [6] and synthesis [7] of folic acid represented the culmination and integration of many apparently divergent paths of investigation. A central purpose of these efforts had been attempts to determine the nutritional requirements of bacteria and animals. It is perhaps now more of historical interest than anything else to mention some of the factors determined in these nutritional studies which have since been identified with folic acid. Some of the more completely studied ones may be briefly mentioned. Day et al.[8] described a deficiency state of monkeys characterized by weight loss, diarrhea, gingivitis, anemia, leukopenia and thrombocytopenia which could be corrected by some substance present in yeast and liver to which the term vitamin M was applied. Hogan and Parrott [9] presented evidence for the existence of an unidentified factor necessary, in addition to the known vitamins for the prevention of anemia in chicks. A factor in liver designated vitamin B_c was found to prevent the development of this anemia. Snell and Peterson [10] reported that *Lactobacillus casei* grown in synthetic medium required the addition of a norite eluate factor, derived from yeast or liver, for maximal growth. Mitchell, Snell and Williams [11] were the first to use the term "folic acid" in referring to a substance derived from spinach and required for maximal growth of *Streptococcus lactis R.* The latter term, folic acid, has, in common parlance, "stuck." One could continue to enumerate additional similar paths of investigation. Suffice it to say that in 1941,

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Hutchings et al.[12] suggested a similarity between the chick vitamins and the bacterial growth factors; and that in 1943 the *L. casei* factor [6] was isolated in crystalline form from liver and was synthesized in 1945.[7] It proved to be a relatively simple organic compound containing the amino acid, glutamic acid, para-aminobenzoic acid and the pterin nucleus. To this compound the chemical term pteroylglutamic acid (PGA) was applied. Popular usage, however, has led to the persistence of the term folic acid which is used synonymously with pteroylglutamic acid.

A series of compounds apparently exists in nature similar to pteroylglutamic acid but differing often from each other solely in regard to the number of glutamic acid molecules which they contain. The commonest form in which the vitamin occurs in food appears to be a compound containing seven molecules of glutamic acid, pteroylhepta glutamic acid.[13] Microbiological assays with *L. casei* and *S. lactis R* indicate that the conjugated vitamin is relatively impotent in stimulating the growth of these organisms in marked contrast with the mono-glutamic acid form.[14] Hydrolysis of the conjugate with release of PGA results in optimal growth. In humans, administration of the conjugate to normal individuals results in the excretion of pteroylglutamic acid.[15] The existence of an enzyme, vitamin B_c conjugase, or more simply conjugase, was postulated and found to occur in abundant amounts in liver, kidney, bone marrow and pancreas.[13] An additional factor to be taken into consideration in this relationship was the demonstration by Bird et al.[16] of the presence in yeast extracts, and probably other foods, of a strong inhibitor of conjugase.

On the basis of available data, it would appear that pteroylglutamic acid occurring usually in conjugated form and accompanied by variable amounts of conjugase inhibitor, is hydrolyzed in the body by the enzyme, conjugase, and thereby liberated for use in metabolic processes chiefly concerned with hematopoiesis but possibly with other body activities. The optimal daily allowance of this nutrient has not yet been determined, nor has the exact mode of its action been ascertained. Several possibilities have been suggested. It has been observed that thymine, a pyrimidine base occurring in nucleoproteins, can be substituted for PGA in the maintenance of optimal growth of *S. lactis R*. Spies and coworkers [17] have reported the successful

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substitution of thymine in large amounts for folic acid in the treatment of several patients with macrocytic anemia. These investigators suggest that folic acid, like other members of the B complex, acts as a co-enzyme in the synthesis of thymine. The studies of Daft [18] suggest that folic acid may play a rôle in nitrogen metabolism.

Recent studies by Bethell et al.,[15, 19] utilizing both free folic acid and the heptaglutamic acid conjugate, shed some light upon the possible physiologic defect in pernicious anemia and related macrocytic anemias. Investigations were made upon a group of patients which included nine pernicious anemias in relapse, two post-gastrectomy macrocytic anemias, and one case each of cirrhosis of the liver and possible non-tropical sprue. In addition, three pernicious anemia patients in remission and seven normal individuals were studied. When pteroylheptaglutamic acid is given orally without conjugase inhibitor to the normal subject, urinary excretion levels for pteroylglutamic acid parallel those obtained after administration of the pure vitamin. The simultaneous administration of conjugase inhibitor and pteroylheptaglutamic acid resulted in lower PGA excretion levels in these persons. The pernicious anemia patients in relapse were studied both in regard to their hematopoietic response and urinary excretion of PGA during the administration of pteroylheptaglutamic acid. When the latter was administered in association with large amounts of conjugase inhibitor, the hematopoietic response was poor and the urinary levels of PGA were low. On the other hand, when the pteroylheptaglutamic acid was administered with lesser amounts of conjugase inhibitor a definite hematopoietic response ensued. Synthetic folic acid administered to these patients likewise resulted in satisfactory hematopoietic responses. Folic acid conjugate was also administered to pernicious anemia patients in remission resulting in the urinary excretion of PGA in amounts approximately equal to those obtained in normal subjects. It was concluded, therefore, that in patients with pernicious anemia there exists an inability to neutralize conjugase inhibitor usually present in most foods containing folic acid conjugate and that as a result a deficiency of folic acid occurs. It was further suggested that one of the pharmacologic actions of liver may be the correction of the metabolic defect in the utilization of naturally-occurring conjugated form of pteroylglutamic acid.

These observations have not yet been repeated and confirmed. Bethell et al. point to the occasional failure of PGA to induce and maintain complete hematopoietic remissions in some pernicious anemia patients; and to the additional important observation that the progression of neurologic disturbances in some individuals is not halted. These facts suggest that the action of liver extract may be more complex than simply to relieve a conditioned nutritional

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deficiency of folic acid. There are now in the literature a number of reports [20, 21, 22] dealing not only with the failure of folic acid to prevent the progression of neurologic disturbances present at the onset of treatment, but with the observation that neurologic disorders of a rapidly progressive type may actually develop during the course of folic acid therapy. Increasing the daily dose of the vitamin to as much as 500 mg. per day did not result in a beneficial effect on the nervous system lesions.[20] Furthermore a rather high incidence of persistent glossitis in folic acid treated patients has also been observed.

There can be no doubt concerning the fundamental biological importance of folic acid in human, animal and bacterial metabolism. In pernicious anemia, folic acid deficiency induced by an inability to utilize the naturally-occurring vitamin conjugate may be an important factor in the production of the anemia. That this is not the only physiologic disturbance in Addisonian anemia is well known. Until the time when all separate manifestations of the disease can be controlled by specific synthetic substances, the use of concentrated liver extracts must continue to be recommended for the treatment of pernicious anemia.

M. S. S.

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REVIEWS

Neutron Effects on Animals. By the Staff of the Biochemical Research Foundation, Dr. Ellice McDonald, Dir. vii + 198 pages; 23.5 × 16 cm. Williams and Wilkins Company, Baltimore. 1947. Price, $3.00.

This book is essentially a collection of papers by a group of investigators attempting to evaluate the biological action and potentialities of neutrons. The first chapter by McDonald outlines the scope and purpose of the project. It points out that when atomic energy is applied industrially, one of the problems will be the protection of workers against the chief by-product "neutron bombardment." For those who wish to refresh their memories and perhaps modernize their concept of the various types of electromagnetic and subatomic-particulate radiation, chapter two is highly recommended.

Chapter three describes the technic involved in the production of neutrons and the exposure of animals to these. The chapters which follow describe the specific effects of neutrons on rats, rabbits, dogs, and various bacteria and other microorganisms. The method of measuring the dosages is somewhat similar to that for measurement of x-rays in that Victoreen ionization chambers are used to measure radiation intensity. The units are expressed, however, as neutron radiation intensity, abbreviated as "n" to distinguish this unit from the roentgen. In these and other studies the biological effect of an n-unit of neutrons is different from that of an r-unit of x-rays even though both give the same reading when measured with a Victoreen 100-r chamber.

In rats the medium lethal dose for neutrons lay between 60-n and 120-n. Neutron doses above 180-n caused death of rats in from six to eight days accompanied by extreme loss of weight and maximum leukopenia. A high percentage of the rats surviving for more than 150 days developed malignant tumors of various types. Attention was called to the fact that no ovarian tumors were observed in the neutron treated rats whereas Furth has reported a consistent induction of ovarian tumors in mice with 50-r of x-radiation. The authors raise the question of whether or not this indicates a difference between the action of x-rays and neutrons. In the reviewer's opinion this would appear to be a matter of differences in the time of observation. Furth's animals developed ovarian tumors approximately one year after radiation. The data given for the rats in this book do not appear to extend over more than 150 days.

Numerous other specific effects of neutrons are described and in general, testicular changes, blood changes, and other physiological effects were similar to those which follow treatment with x-rays and gamma radiation. Since the gamma radiation was screened out by three inches of lead, these effects could not have been due to radiation of this type. The authors seem to have been impressed, however, by the fact that neutrons have a greater biological effect than gamma and x-radiation.

As admitted in the preface, this book has barely scratched the surface as far as future developments are concerned. The separate contributions which make up this volume are too specific for the book ever to become valuable as an elementary reference in this field, but they should serve to stimulate future work along lines that will undoubtedly assume greater importance in medical diagnostic and therapeutic procedures.

F. H. J. F.

Paravertebral Block (in Diagnosis, Prognosis, and Therapy: Minor Sympathetic Surgery). By FELIX MANDL, M.D., F.I.C.S., Professor of Surgery, Hadassah University Hospital, Jerusalem. Translated by GERTRUDE KALLNER, M.D. Foreword by MAX THOREK, M.D., F.I.C.S., Professor of Surgery, Cook County Graduate School of Medicine, Chicago. 330 pages; 23.5 × 15.5 cm. Grune and Stratton, New York. 1947. Price, $6.50.

This is an excellent monograph dealing with paravertebral block, both as a therapeutic measure and as a method of differential diagnosis. The author discusses the anatomy and physiology of the sympathetic system, and their relationship to the technic of paravertebral injections. Numerous case histories are cited, with an analysis of both satisfactory and unsatisfactory results. The results of paravertebral block are discussed and compared with those of other methods. To all physicians interested in paravertebral block this book will serve as an excellent reference.

G. H. Y.

Peripheral Vascular Diseases (Angiology). 2d Ed. By SAUL S. SAMUELS, A.M., M.D., Consulting Vascular Surgeon, Long Beach Hospital, Long Beach, New York; Attending Vascular Surgeon, Brooklyn Hospital for the Aged; Chief of the Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic Hospital, New York; Fellow in Surgery, New York Academy of Medicine; Member of Committee on Surgery, New York Diabetes Association. 85 pages; 22 × 14 cm. Oxford University Press, London, New York, Toronto. 1947. Price, $2.50.

This is a concise outline of peripheral vascular diseases, that also includes outlines of the anatomy of the vascular system and of the autonomic nervous system. A concise classification of peripheral vascular disease is given with an excellent résumé of the symptomatology of peripheral arterial disease and of the objective signs of arterial occlusion. Each disease entity is individually and briefly outlined, and valuable therapeutic suggestions are given.

G. H. Y.

The Selected Writings of Benjamin Rush. Edited by DAGOBERT D. RUNES. 433 pages; 21 × 14 cm. Philosophical Library, New York City. 1947. Price, $5.00.

To those physicians interested in medical history and to those who particularly admire the writings of Benjamin Rush, this volume will be a source of enjoyment and one which will find a welcome place in their private libraries.

These selected writings of Benjamin Rush serve to emphasize his profound learning and his skill in observation. They indicate also the breadth of his interests which extended beyond his classic contributions to the field of medicine to such fields as government, education, religion and natural history. One gains in reading this book a deeper insight into the mind and culture of this great physician and champion of the American Revolution.

The frontispiece is a reproduction of the fine engraving of Benjamin Rush by William Haines. The appendix contains a list of writings published during his lifetime and a selected bibliography. There is an adequate index.

J. E. S.

BOOKS RECEIVED

Books received during December are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

American Medical Research, Past and Present. By RICHARD H. SHRYOCK, Ph.D., Professor of History and Lecturer in Medical History, University of Pennsylvania, etc. 350 pages; 21.5 × 14 cm. 1947. The Commonwealth Fund, New York. Price, $2.50.

American Pharmacy: Advanced Pharmacy—Medical, Surgical and Dental Supplies—Animal Health Pharmacy (Vol. II). Editor-in-Chief: RUFUS A. LYMAN, M.D., Director, School of Pharmacy, University of Arizona. 379 pages; 26 × 18.5 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $7.00.

Congenital Malformations of the Heart. By HELEN B. TAUSSIG, M.D., Associate Professor of Pediatrics, Johns Hopkins University School of Medicine, etc. 618 pages; 26 × 18 cm. 1947. The Commonwealth Fund, New York. Price, $10.00.

The Contemporary American Family. By ERNEST R. GROVES and GLADYS HOAGLAND GROVES. 838 pages; 22.5 × 15 cm. 1947. J. B. Lippincott Company, Philadelphia. Price, $4.50.

400 Years of a Doctor's Life. Collected and arranged by GEORGE ROSEN, M.D., and BEATE CASPARI-ROSEN, M.D. 429 pages; 23.5 × 16 cm. 1947. Henry Schuman, New York. Price, $5.00.

Gynecological and Obstetrical Urology (2d Ed.). By HOUSTON S. EVERETT, A.B., A.M., M.D., Associate Professor of Gynecology, The Johns Hopkins University, etc. 539 pages; 24 × 16 cm. 1947. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Hormones and Behavior: A Survey of Interrelationships Between Endocrine Secretions and Patterns of Overt Response. By FRANK A. BEACH, Professor of Psychology, Yale University; with a Foreword by EARL T. ENGLE. 368 pages; 24 × 16 cm. 1948. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $6.50.

The Parathyroid Glands and Skeleton in Renal Disease. By J. R. GILMOUR, M.R.C.P., Pathologist in Emergency Medical Service, Junior Assistant Director, Bernhard Baron Institute of Pathology, London Hospital. 157 pages; 22 × 14 cm. 1947. Oxford University Press, New York. Price, $5.75.

Practical Office Gynecology. By KARL JOHN KARNAKY, M.D., Assistant Professor of Clinical Gynecology, Baylor University College of Medicine, etc. 261 pages; 26 × 18 cm. 1947. Charles C. Thomas, Springfield, Illinois. Price, $7.50.

Radium Dosage: The Manchester System. Compiled from Articles by RALSTON PATERSON, F. W. SPIERS, S. K. STEPHENSON, H. M. PARKER, M. C. TOD, and W. J. MEREDITH. Edited by W. J. MEREDITH, M.Sc., F.Inst.P., Christie Hospital and Holt Radium Institute, Manchester. 124 pages; 26 × 19 cm. 1947. The Williams and Wilkins Company, Baltimore. Price, $4.50.

Teaching Psychotherapeutic Medicine: An Experimental Course for General Physicians. Edited by HELEN LELAND WITMER, Ph.D.; Introductory Chapter by GEDDES SMITH. 464 pages; 24 × 16 cm. 1947. The Commonwealth Fund, New York. Price, $3.75.

COLLEGE NEWS NOTES

Additional Life Members

The American College of Physicians takes especial pride in announcing the addition to the Roster of Life Members of the College of the following Fellows, as of the dates given.

Maurice Kovnat, Miami Beach, Fla., December 15, 1947
Edgar Wayburn, San Francisco, Calif., December 22, 1947
Ross Paull, La Jolla, Calif., December 26, 1947
Lawrence E. Geeslin, Jacksonville, Fla., December 29, 1947
George Baehr, New York, N. Y., January 3, 1948
Worth B. Daniels, Washington, D. C., January 3, 1948
S. Douglas Craig, Winston-Salem, N. C., January 5, 1948
Leon Bromberg, St. Louis, Mo., January 5, 1948
Frederic T. Billings, Jr., Nashville, Tenn., January 9, 1948
Herman A. Dickel, Portland, Ore., January 9, 1948
Leon S. Lippincott, Daytona Beach, Fla., January 10, 1948
Marsh McCall, New York, N. Y., January 10, 1948
Joseph F. McVeigh, Fort Worth, Tex., January 10, 1948
Donald E. Forster, Portland, Ore., January 12, 1948
I. S. Kahn, San Antonio, Tex., January 12, 1948
Carl S. Leede, Seattle, Wash., January 12, 1948
Carlyle Morris, Metuchen, N. J., January 12, 1948
F. Sullivan Hassett, Elmira, N. Y., January 13, 1948
Edward Weiss, Philadelphia, Pa., January 13, 1948
Charles C. Wolferth, Philadelphia, Pa., January 13, 1948

Notice of Proposed Amendment to the Constitution of the American College of Physicians

The By-Laws of the College were amended at the 1947 Annual Session of the College, and, among other things, provided a new Article VI for the election of Masters, in which it is specified, "a special Committee on Masterships will be named by the President. This Committee will consist of two members from the Board of Regents and one member from the Board of Governors. It will bring in nominations of Master to the Board of Regents for election or rejection."

That amendment makes it necessary for an amendment to the Constitution, Article IV, (b), substituting in line 5, "Committee on Mastership" in the place of "Committee on Credentials." Namely; this paragraph shall be amended to read:

"Masters of the American College of Physicians shall be those who have attained the rank of Fellows, and who on account of personal character, positions or influence and honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine, are recommended by the Committee on Masterships to the Board of Regents for special and well-earned distinction. Such Masters shall be designated as Masters of the American College of Physicians, and shall be authorized to use the letters M. A. C. P. in connection with scientific publications, at professional and academic functions and in connection with their professional activities."

This amendment shall be submitted to the members at the next annual business meeting at San Francisco, April 22, 1948, for approval.

American Trudeau Society Announces Courses in Thoracic Diseases

The American Trudeau Society announces the following postgraduate courses in thoracic diseases:

March 22–26, 1948—Herman Kiefer Hospital, Detroit, Mich. (Detroit Department of Health and Wayne University College of Medicine cooperating); Chairman, Dr. Paul T. Chapman, Herman Kiefer Hospital; fee, $50.00.

March 22–27, 1948—North Carolina Sanatorium, Sanatorium, N. C. (Medical Schools of University of North Carolina and Duke University cooperating); Chairman, Dr. Henry Stuart Willis, North Carolina Sanatorium; fee, $50.00.

April 5–17, 1948—Boston, Mass. (Medical Schools of Harvard, Tufts and Boston Universities cooperating); Chairman, Dr. Theodore L. Badger, 264 Beacon St., Boston, Mass.; fee, $100.00.

April 12–24, 1948—Plans not yet completed but course will be held at Dallas, Tex.; Chairman, Dr. Julius L. Wilson, 1430 Tulane Ave., New Orleans 13, La.; fee, $100.00.

Postgraduate Assembly in Endocrinology

The Association for the Study of Internal Secretions announces through Dr. E. Kost Shelton, F.A.C.P., Chairman of the Committee on Postgraduate Instruction, a Postgraduate Assembly in Endocrinology at Los Angeles, February 23–28, 1948. Many outstanding students of endocrinology in the United States and Canada appear on the faculty. Applications should be filed with Dr. Shelton at 921 Westwood Boulevard, Los Angeles 24, Calif.

American College of Radiology Offers Two Postgraduate Courses

The American College of Radiology will offer courses in radiology at Philadelphia, February 2–6, 1948, under the joint sponsorship of the College and the Philadelphia Roentgen Ray Society, and at Chicago, March 8–12, 1948, in collaboration with the Chicago Roentgen Society. Fee will be $50.00 for each course. Details are available through the American College of Radiology, 20 N. Wacker Drive, Chicago 6, Ill.

The Interamerican Society of Cardiology has authorized the meeting of the III Interamerican Cardiological Congress, to be held in Chicago, Illinois, at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the American Heart Association annual meeting, June 18 and 19, and the American Medical Association meeting the week of June 20. Inquiries regarding the Congress may be addressed to the offices of the III Interamerican Cardiological Congress, at the Michael Reese Hospital, Chicago, Illinois.

Cornell University Medical College celebrates its Fiftieth Anniversary this year. The Alumni Day will be held on March 11 at the College, and is of special significance to all of our alumni. The program will include registration in the morning, with luncheon at the Nurses Residence, to be followed by the business meeting and a schedule of rounds and conferences in all departments. Dinner will be served at the Roosevelt Hotel and dancing will conclude the day.

Dr. Arden Freer Succeeds Dr. Paul R. Hawley as College Governor for the Veterans Administration

Due to the resignation of Dr. Paul R. Hawley, Chief Medical Director of the Veterans Administration and also as the College Governor for the Veterans Administration, the Deputy Medical Director, Dr. Arden Freer, F.A.C.P., has been appointed by President Hugh J. Morgan of the College as Governor for the Veterans Administration until the next regular election. Effective January 1, 1948.

It was recently announced that Dr. Hawley will undertake on April 1, 1948, the position of Chief Executive Officer of the Blue Cross and Blue Shield health service plans. Dr. Hawley's offices will be in Chicago.

Grateful acknowledgment is made of the kindness of Herbert T. Kelly, M.D., F.A.C.P., Philadelphia, Pa., for his contribution to the College Library of Publications by Members of a copy of the new 5th edition of "Simplified Diabetic Management," by Joseph T. Beardwood, Jr., M.D., F.A.C.P., and Dr. Kelly. This book was published by the J. B. Lippincott Company, Philadelphia.

Dr. Joseph T. Roberts, F.A.C.P., formerly Chief Medical Officer in the Department of Medicine, Gallinger Municipal Hospital, Washington, D. C., has been appointed Dean of the University of Arkansas School of Medicine at Little Rock, having assumed his duties there during the autumn of 1947.

News from Puerto Rico

Luis M. Morales, San Juan, Puerto Rico, has been elected a member of the Council of the National Committee for Mental Hygiene.

The following Fellows of the College were among the speakers of the 44th Annual Meeting of the Medical Society of Puerto Rico, which was held at San Juan, December 10–14, 1947: Drs. Richard A. Kern and William D. Stroud, Philadelphia; Dr. Cecil J. Watson, Minneapolis, Minn.; Dr. Charles F. McKhann, Cleveland, Ohio; Dr. Louis Krause, Baltimore, Md.; Dr. Solomon Katzenelbogen, Washington, D. C.; and Drs. Roberto Francisco Azize, Rurico S. Diaz-Rivera, Federico Hernandez-Morales, Ramón M. Suárez, and Enrique Koppisch, all of San Juan. The Chairman of the program Committee was the College Governor for Puerto Rico, Dr. Suárez.

ABRIDGED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA.

NOVEMBER 23, 1947

THE regular autumn meeting of the Board of Regents was held at the College Headquarters, Philadelphia, Pa., beginning at 9:50 a.m., November 23, 1947, with President Hugh J. Morgan presiding, and the following in attendance:

Hugh J. Morgan	*President*
Walter W. Palmer	*President-Elect*
Reginald Fitz	*First Vice President*
Francis G. Blake	*Second Vice President*
William D. Stroud	*Treasurer*
George Morris Piersol	*Secretary-General*
Walter B. Martin	
William S. Middleton	
James E. Paullin	
LeRoy H. Sloan	
Ernest E. Irons	
William S. McCann	
T. Grier Miller	
Charles F. Moffatt	
Charles F. Tenney	
David P. Barr	
A. B. Brower	
Alex. M. Burgess	
Ernest H. Falconer	
Cyrus C. Sturgis	
Maurice C. Pincoffs	*Editor,* ANNALS OF INTERNAL MEDICINE
Walter L. Palmer	*Chairman, Board of Governors*
Edward L. Bortz	*Chairman, Advisory Committee on Postgraduate Courses*
William J. Kerr	*Chairman, 29th Annual Session*
Edward R. Loveland	*Secretary, Board of Regents*

The Secretary, Mr. E. R. Loveland, read abstracted Minutes of the preceding meetings, which upon motion were approved as read.

Among the more important communications presented by the Secretary were the following:

A cablegram from the Royal Australasian College of Physicians, informing the College that President Hugh J. Morgan had been unanimously elected an Honorary Fellow of that College;

Notice from the Gorgas Memorial Institute of Tropical and Preventive Medicine, advising of the election of President Hugh J. Morgan to the Board of Directors of that institution;

A notice from the Executive Committee of approval of the reassignment of the Governors' territorial areas of Eastern and Western New York, the new division providing that Western New York be enlarged to include all of Northern New York and East to Albany, then extending diagonally Southwest to Binghamton and then directly South to the Pennsylvania border;

A report on the approval by the Executive Committee, through President Morgan, of the Medical Library Association's project to provide adequate abstracting and indexing of medical literature;

A recommendation from Dr. George F. Strong, Regent, that the Provinces of Manitoba and Saskatchewan be separated from the present area, which includes also Alberta and British Columbia, and that a separate Governor be elected to represent Manitoba and Saskatchewan. (The Board of Regents approved the recommendation by formal resolution.);

A reminder that the American College of Physicians a year ago agreed to participate in the Fourth International Congress on Tropical Medicine and Malaria, sponsored through the State Department and to be held in this country in 1948, with the subsequent appointment of Dr. Joseph M. Hayman, Jr., of Cleveland, as the official representative of the College. Said Congress will be held in Washington, May 10–19, 1948, and by formal resolution, the Regents voted to defray such traveling expenses as Dr. Hayman may have in connection with this appointment;

Report of the approval by the Executive Committee of an increase, amounting to about 8 per cent, in the printing costs of the ANNALS OF INTERNAL MEDICINE as of August 1, 1947, said action being formally approved by the Board of Regents;

A notice from Dr. William S. McCann, F.A.C.P., Chairman of the American Board of Internal Medicine, of his intention to resign from that Board as of June 30, 1948, requiring a new appointment by the College to fill out his unexpired term.

Dr. George Morris Piersol, Secretary-General, reported the deaths of two Masters and 37 Fellows since the preceding meeting of the Board, said names being spread upon the Minutes; also the addition of 18 Fellows as Life Members, whose names also were spread upon the Minutes.

President Morgan pointed out that among those who had died were two past Presidents, Doctors Ernest B. Bradley and John H. Musser, and one former Governor, Dr. Fred W. Wilkerson. He requested Doctors James E. Paullin and David P. Barr to prepare an appropriate memorial on Dr. Ernest B. Bradley, to appear in the ANNALS, to be spread on the Minutes and to be sent to Dr. Bradley's family; Doctors William S. Middleton and T. Grier Miller to prepare the memorial on Dr. John H. Musser; and Doctors Walter L. Palmer and Walter B. Martin to prepare a memorial on Dr. Fred W. Wilkerson.

Dr. Piersol, as Chairman of a Committee of three, suggested the following legend for the diploma for the Alfred Stengel Memorial Award, and suggested that it be engrossed each year, because it would be impractical to have a diploma which could be struck off in quantity, since this award will be given as a very special honor from time to time and should be individualized in each instance to meet the particular occasion.

THE AMERICAN COLLEGE OF PHYSICIANS

THE ALFRED STENGEL MEMORIAL AWARD

This Award, made available through the generosity of James D. Bruce, a former Regent and President of the College, is awarded by the Regents of the American College of Physicians to

.....M.D., F.A.C.P.

in recognition of his many years of loyal and devoted service to the College and .....

Conferred at ..... on .....

.....

President

.....

Secretary-General

The Board of Regents formally approved the proposal and copy by resolution.

Dr. Ernest E. Irons, reporting for a special Committee appointed by the President, including also Doctors George H. Lathrope, J. Edwin Wood, Jr., Reginald Fitz and Edward L. Bortz, to present nominations for the Alfred Stengel Memorial Award, submitted five nominations, which were voted upon by secret ballot. The nominee (whose name may not be announced until the next annual Convocation) was unanimously selected.

At this point members of the Board of Regents personally, through Dr. James E. Paullin, presented to Miss Pearl M. Ott a beautiful Hamilton wrist watch, with appropriate engraving on the reverse side, in recognition of her twenty-first anniversary of service to the College and of the affection of the Officers and Regents.

Mr. E. R. Loveland, the Executive Secretary, presented his annual fall report, dealing with the 25 Regional Meetings conducted during the autumn, Postgraduate Courses and other administrative activities. He asked for direction from the Board with regard to the publication of a new and revised Directory of the College, or a new Membership Roster, during 1948. Due primarily to the excessive cost and shortage of paper, the Board of Regents by resolution voted to publish a Membership Roster instead of a full Directory, but to include therein the Constitution and By-Laws and other necessary announcements concerning Fellowships, Awards and other activities of import to members.

Report, American Board of Internal Medicine—Dr. William S. McCann, Chairman: Mr. President and members of the Board of Regents, the Board has chiefly to report a lot of perplexities and problems concerning which it desires more light. The American Board of Internal Medicine, in common with other specialty boards, has long prescribed the program of training to be followed for admission to its examination. In order to accomplish this, it is necessary to set some mark of approval on the hospitals at which a candidate may expect to get his necessary training. Since the War, the task of examining training facilities has become so onerous that the machinery for doing this has almost broken down, due to the large number of veterans who are seeking certification and the host of new hospitals that have set up residency training programs and are seeking approval. The Council on Medical Education and Hospitals of the American Medical Association has been the agency in the past which has accumulated the data and inspected the facilities. Its surveys, when completed, are submitted to the Board for acceptance, but even with the large facilities of the American Medical Association, the task has lagged behind and the American Board is bedeviled with complaints about delays and things of that sort. There are complaints from another angle, from the Deans and Faculties of schools who generally protest that our rather rigid requirements are setting a strait-jacket on medical education. They say the young men are forming a line and proceeding in lock step toward the goal of certification, and that they no longer enter educational institutions to learn anything. They simply want to be certified.

The American Board of Internal Medicine is acutely conscious of the justice of many of the complaints, and it has endeavored to liberalize its requirements. A plan was drawn up, which you probably have all seen. It was published in the Journal of the American Medical Association and in the ANNALS OF INTERNAL MEDICINE within the past year. Some members of the Board, who felt that the liberalization and the diversification and means of getting training were good, feel they do not go far enough, and at our last meeting we had a serious debate on the subject of doing away with the whole business of approval of training agencies and simply going back to certain basic requirements which a candidate would have to meet in order to be examined—his professional qualifications, licensure and a certain period of time following graduation. That sort of move would throw the burden of responsibility onto the candidate himself to decide where he could get adequate preparation for the examina-

tion, and I suppose in a way it could be defended, because the superior man certainly can judge the quality of the training that he gets. The inferior man may not do so, but we are not so much interested in him. The Board in that case would become purely an examining body.

There was a sharp division in the Board, and it became obvious that we could not take any drastic action of this kind, but if we are to continue some sort of supervision of the training program, it is obvious that it has got to be put into the hands of somebody of comparable jurisdiction that can provide inspection and has the personnel and facilities for carrying on inspection and scrutiny of the training agencies.

It is certainly true that that task is too great for the American Board of Internal Medicine to perform. All that we know about these agencies is what we get on paper, summarized for us by the Council, and, in view of the volume of work which has fallen on the Council, it has been impossible for them to keep abreast of the needs. If I could offer a suggestion, I would say that I think whatever body undertakes it might well be a joint creature of the College, the American Medical Association and the Association of American Medical Colleges. I believe if the latter body were included in the formation of the approving machinery, it would dispose of the problem which we now have of meeting the educational ideas of Deans and Faculties of the schools. Certainly they are entitled to their ideas and to consideration.

I think I can say that the Association of American Medical Colleges is going into a new phase. It has increased its income by raising the dues to the member Colleges, and it is going to cut down the expenditures of money on publishing a magazine; it is due to get a new Director or Secretary, who can be chosen for his vigor and youthful enthusiasm, and it is possible that this body could be made to perform a very useful function. I hope that this Board of Regents will give thought to this matter and will give us the benefit of its advice through discussion.

PRESIDENT MORGAN: There are two aspects of the Chairman's report; first, the liberalization of the requirements by the American Board of Internal Medicine for eligibility to examinations, and, second, proposed change in the surveying machinery. Requirements have been liberalized to the point that except for the time factor any one who practices Internal Medicine approximately ten years may come up for examination, regardless of the nature of that practice. If he follows the advice of the Board relative to type of work that he does and particular training experience through which he puts himself, he will qualify for eligibility for examination and will render himself eligible that much sooner. There has been a very marked liberalization; no one who is seriously interested in practicing Internal Medicine now is excluded from examination.

DR. MAURICE C. PINCOFFS: I think it would be a very unfortunate thing if some form of inspection and approval of the facilities for postgraduate education were given up. First, I do not think we can rely on the wisdom of these young men after an internship to judge wisely what is the best type of training. Many of them would go to hospitals in which their financial burden would be somewhat lightened, feeling that perhaps while it is not the best, the financial recompense makes it feasible for them to stay there longer; second, the Board's requirements have entered into the practice of American medicine to an astonishing extent, and I speak now from the point of view of what it has done to standards in hospitals, other than primarily in school hospitals. The strength of the present Veterans Administration is largely through an affiliation with medical schools, and thus meeting the requirements for training. They get many capable young men that they would not otherwise get. The Army has set up five General Hospitals for postgraduate training of their members, and they were forced to do this, to a certain extent, by the attitude of young men who wished to have this training in accordance with Board standards. That movement in the Army is going to have a very large influence on the medical care that some million of our young citizens receive.

It goes further than that. State institutions of all kinds are thinking seriously of how they can raise their standards. Tuberculosis hospitals in the State of Maryland are contemplating trying to raise the hospital nearest Baltimore to standards acceptable to the American Board of Internal Medicine and the American Board of Surgery. Only if they can do that, do they feel they are going to begin to solve their personnel problem.

All through the country the action of the Boards in stimulating enthusiasm in young men for better training has reacted on the level of medical care in many ways in many institutions. I feel that if it was simply said that when a candidate feels ready to come up for the examination, he can do so, and we shall depend solely on the examination, that much of the value of what has been accomplished might be lost in the next decade.

DR. IRONS: I am quite in agreement with Dr. Pincoffs. The effect of the American Board of Internal Medicine on medical education in this country is far beyond what many of us expected and beyond what the College even envisioned when the Board was established. The net result is an admirable accomplishment of the College. With respect to the requirements of the Board, they have been modified from time to time. At the beginning, the Board had to feel its way, but the present Board has enormously improved the mechanism of examination. Requirements in preparation for examination were set up almost entirely with the idea of protecting the candidate. It was recognized that what a young man does in the first five years after graduation largely determines what place he is going to occupy in the future. Therefore, the requirements of the Board have almost been made up with the idea of protecting the candidate. Several years ago the Board thought many men could obtain a good preceptorship with men well able to enlarge their studies, while working on the job. It was an admirable provision. The Board did its best to select proper preceptors, but after several years' experience learned that some of these preceptors were not carrying out the ideas of the Board and were profiteering on the candidate. There was nothing for the Board to do except abolish preceptorships for a time—you couldn't hold a trial for each preceptor. It then became necessary to set up a new group of requirements which vastly liberalized the program by which anybody can get the necessary training, if he is willing. However, the majority won't do it, under this eight and ten-year program, except the unusual case. That democratizes the examination, to meet the criticisms of the Board.

I would be much distressed to see the Board do away with all requirements, because after all we all still have a responsibility to the young man who is entering on his life work. To remove all requirements will set this matter back where it was before the Board came into existence. There has been a tremendous lot of criticism hurled against the Board—most of it unjust. Anybody who sets up standards will be subject to criticism. I want to congratulate the Board on its performance up to date, and recommend that on no account should they do away with the requirements.

DR. FRANCIS G. BLAKE: Mr. President, accepting without question the great accomplishments of the Board in raising standards in Internal Medicine and raising standards in residency training programs in an increasing number of hospitals, it seems to me, as Dr. McCann has pointed out, that there are two very urgent problems that must be met. The recent steps in liberalization seems to me to have met to a considerable extent the criticism of the lock step training program. As times goes on, there will be room for more liberalization, but, first, there are nowhere near enough approved residency trained physicians to take care of those who want to qualify themselves for recognition. Means for establishing an adequate residency training program must be provided for a large body of men.

DR. PAULLIN: Mr. Chairman, may I ask Dr. Blake to give us some statistical data on the inadequacy of approved residencies in medicine—that is, the approximate

number of people who cannot get proper training that would qualify them for certification? My impression is that the number is not very large. I hear few complaints from the surgeons who greatly outnumber the internists. I should hate to alter the past policies of the Board in this regard, even though momentarily some men cannot get training. Many Veterans' Hospitals, as now established, have met requirements; numerous hospitals in some of the cities which five years ago were not approved have raised their standards to the point where they are temporarily approved for residency training. I think it would be an awful mistake if we receded from our present standards and allowed almost anyone after ten years to take the examination. We have brought a lot of these hospitals up to a standard which they never had before. They are rendering better medical care and better medical service, and I personally doubt if the few individuals who lack the opportunity of getting training would ever qualify for certification anyhow.

DR. REGINALD FITZ: I cannot help but interject something here, for I have been a member of the Council and a member of the Board for many years, and more recently a member of the College Committee working with the Council. I think the College's considerations here are terrific. As Dr. Paullin says, there are a whole host of young men who think they want to be internists, yet not all of them are going to be capable of attaining certification. In connection with the question of establishing residencies, which has been a fine thing, there are many hospitals that think they would like to offer approved residencies, and the result is that, with the War doing away with many of the Council inspectors, we have been trying to re-establish our machinery and to resume the plan of having the participation of the Board and the Committee of the College with the Council. All of this takes a great deal of time, but is a good thing. I hope we will all be patient, because I am perfectly sure that Dr. Paullin is right when he says we will do more harm by trying to do things too quickly than by putting up with a certain number of people who do not like the way we are doing it; we must make sure we are doing it right, because there is no question in my mind that if the hospital is approved for residency training in Internal Medicine it ought to be good, and that should be determined, even though it takes an extremely long time. With the College, the Board and the American Medical Association all working together, we are doing a pretty good job.

DR. IRONS: It was the War that brought about most of the immediate troubles to the Council. The Council was cut down to one inspector a year or so ago, and now has four and is looking for more. As soon as that increased personnel begins to be felt, some of the delays and difficulties that Dr. McCann mentions will be eliminated.

DR. PINCOFFS: I feel very strongly, as has been mentioned by others, that the present system of supplying opportunities for these young men is hampered by the slowness of inspection. I also question whether the inspections are always as satisfactory as they should be. There is a question whether the young men appointed as inspectors by the Council are really the best judges always of the type of educational opportunities the hospital should provide. I have heard the criticism that the Council and the Board, through their action, have taken too dominating a position as to the character of postgraduate education leading to specialization, that there should be something, in some more official way, represented in the inspection of schools and hospitals. I was struck by Dr. McCann's suggestion of bringing in the Association of American Medical Colleges, which I think is in line with the functioning of schools having a voice in their own communities and environments, either in approving or disapproving institutions or personnel for the character of professional work. The local use of this body within its own region deserves study. They often know quite intimately the attending staff of a hospital and the standards of work done in it.

DR. DAVID P. BARR: I wish to make reference again to the question of liberalization. I hope that in the consideration of the Board one may regard or may take ac-

count of the developments in various directions which have not in the past been classified as Internal Medicine. I am thinking particularly of health services, such as are now established in many of our great universities—examples being Harvard, Cornell, Michigan, Minnesota—services in special hospitals not previously regarded as part of Internal Medicine. There I have particularly in mind the development of the Memorial Hospital, a special cancer hospital, of which there is now contemplated a very extensive development in Internal Medicine. Then, there are categories of fellowships that have not previously been thought of as Internal Medicine, and I have in mind there the psychosomatic fellowships that are being established at Cornell and Harvard. They are being established also in Cincinnati and Rochester. All of these things represent training which could at least, in some instances, be regarded as equivalents of residencies in Internal Medicine as such and, while each must be judged on its merits and the character of the training; should be taken into account.

PRESIDENT MORGAN: The Board does find itself in a very difficult position, having actually claimed the responsibility from the point of view of approving hospitals as proper places for training. It finds itself with no mechanisms to inspect those hospitals and no one obviously can develop such a mechanism unless it opens up a new field altogether, and more or less does in medicine what the College of Surgeons does in surgery. Therefore, the American Board has depended mainly upon the American Medical Association's Council and its inspectorial activities. That has been the nub of the situation, and the Council has had its difficulties. One of the most important things that the American Medical Association can do is to really energize and step up that activity and bring it to an adequately high level. If the Council is to be the actual body to survey and approve hospitals, anything that will broaden its influence will be an advantage. There is a tremendous hospitalization program under way by the Government, and it will be very much under the influence of Government agencies. The broader the point of view that can be exhibited in relation to these developments, as pointed out by Dr. Barr, the wiser will be the administration.

DR. MCCANN: I think I agree, and while already on record as having been in favor of doing away with any responsibility for the previous training of candidates, I would now retreat from that position and say that I think we are committed to some sort of supervision and guidance from those agencies. The only agency that seems to be competent to do this is the American Medical Association, but I would like to urge upon the members of the Council on Medical Education and Hospitals and the Liaison Committee of this College that they explore the extent to which they can supplement their facilities by bringing in the Association of American Medical Colleges. I agree with Dr. Pincoffs that they would add some senior wisdom to the work which the inspectors of the Council do, and would provide them with certain information which would be invaluable. The Deans and Faculties know the local facilities and where qualifications are met. With the addition of this help, we could get the job done and done in a broad minded way that would let a man preparing himself as an internist take some time to train himself also in psychiatry or in pediatrics. I think the biggest lack of the internist today is of knowledge of pediatrics.

DR. PAULLIN: Has not the American Board of Internal Medicine sufficient money to finance, for two or three years, somebody to work with the Council and help the inspection program?

DR. MCCANN: It might be worked out.

DR. PAULLIN: Most of the members of the Council are Deans of medical schools. Now we would have somebody approaching from the other side.

DR. MCCANN: The assets of the American Board of Internal Medicine are somewhere around $65,000.00 or $75,000.00, which is roughly the amount of money we possess. We have increased the fee for the examination, because the costs are rising. I haven't any idea what it would cost to help the Council.

DR. FITZ: I do not think it is a question of money so much as getting personnel. Recently we had a group of about 125 veterans taking a course at Harvard and I tried to tell them what the possibilities were and what I thought was an interesting temporary job, namely, learning to analyze and inspect hospitals for those that would like to take a course in educational administration. I received about a dozen names, but in the end they all got something else that they preferred to do. It is very difficult to get first-rate men. They find greater opportunities in other fields.

DR. IRONS: The Board of Trustees of the American Medical Association is perfectly willing to furnish whatever money is necessary, but cannot get the personnel.

DR. PAULLIN: The question is of getting the American Board interested, so that they would see it in a different situation.

. . . On motion by Dr. LeRoy H. Sloan, seconded and regularly carried, it was

RESOLVED, that this matter by informal discussion be explored by the College with its friends in the other organizations, the Council on Medical Education and Hospitals, the American Board of Internal Medicine and the Association of American Medical Colleges.

Dr. George Morris Piersol, Chairman, reported for the Committee on Credentials on the following matters:

The new method of circularizing members by distribution of a Roster of Candidates had proven satisfactory, but the Committee pointed out that it does not wish the return of the Roster of Candidates, but desires to have individual letters concerning any candidate about whom any Fellow has any doubt regarding his personal or professional qualifications;

The Committee on Credentials feels that the College can recognize only the regularly constituted Boards for Certification of Specialists, and cannot include various and sundry boards which may spring up among special groups;

A case in point was brought up of a former Associate who had been dropped for failure to qualify for Fellowship within the period prescribed by the By-Laws. The Committee pointed out that modification of the rules and By-Laws passed at the last Annual Session makes it impossible for such candidates who have been dropped from Associateship for reason to be nominated for direct Fellowship, but that they may be privileged to be proposed again for Associateship;

Dr. Ralf S. Martin, Portland, Maine, was reinstated to Associateship; the application of a former Fellow for reinstatement was denied;

The Committee had reviewed during the two previous days credentials of 284 candidates for Associateship and 187 candidates for Fellowship. The analyses of its recommendations follow:

Candidates for Associateship:

Recommended for Election		188
*Fellowship Candidates Recommended for Election first to Associateship		5
Deferred		52
Rejected		44
		284, plus *5

Candidates for Fellowship:

Recommended for Advancement to Fellowship	93	
Recommended for Election Directly to Fellowship	14	107
*Recommended for Election first to Associateship		5
Deferred		58
Rejected		17
		187

On recommendation of the Committee and formal approval by resolution of the Board of Regents, 193 candidates were elected to Associateship and 107 candidates were elected to Fellowship (this list appeared in the January, 1948 issue of this journal).

The Committee presented the following analysis of the group of Associates elected five years previously, December 13, 1942:

Already Advanced to Fellowship	92
Dropped for Failure to Qualify	21
Time Extended Due to Military Service	39
Total Candidates Elected, 12–13–42	152

The names of those dropped for failure to qualify and the names of those whose Associate terms were extended, due to military service, were recorded in the formal Minutes. Likewise, the names of 7 Associates elected prior to December 13, 1942, but whose Associate terms, previously extended due to military service, had now expired, were recorded in the formal Minutes.

The Committee presented the following recommendations for later consideration by the Board of Regents, due to their involving very far-reaching and fundamental questions:

"(1) The Committee realizes that the number of applicants for admission is growing steadily. The question comes up from time to time about a candidate who is not an internist, but is a neuropsychiatrist, a dermatologist, or some other affiliated specialist. The informative booklet of the College says that membership need not be made up only of internists, but may include those properly qualified in pediatrics, neurology, psychiatry, public health, radiology, etc.

"The Committee believes it would be well to seriously consider changing our regulations and limiting membership in this organization to those who are internists and to discontinue after a certain time to take in men who are not internists, even though they be engaged in affiliated specialties. The Committee makes this recommendation primarily to further limit the size of the College. These affiliated specialties all have their own certifying boards and their own special societies, and the Committee questions whether radiologists, dermatologists, and a few others, ever take a very vital interest in the College. They are amiable and distinguished people who are in purely scientific branches, a little different from strict internal medicine.

"(2) In spite of explanatory and clear definitions which the Survey Committee made and were incorporated as amendments to our By-Laws last year, it is still a very difficult matter from data available to come to a conclusion as to who is an internist, and whether he is a man who will ultimately be able to attain certification. Even those members of the Credentials Committee who are most violent in their opposition to the recommendation some of us made, namely, that before a man should be considered as an Associate he should be certified by the American Board of Internal Medicine, have come to the conclusion that such a rule wouldn't be too objectionable, after all, if we could limit the membership of the College to those who are internists. If we decide to take only internists, we can only recognize those who have already been certified, and many difficulties would be solved and hours of debate would be eliminated.

"The Committee feels that it would make for a much stronger and more homogeneous organization."

On the nomination and recommendation of the Committee on Masterships, Dr. William S. Middleton, Chairman, the five following Fellows were unanimously elected Masters of the College:

Dr. O. H. Perry Pepper, Philadelphia, Pa.
Dr. James E. Paullin, Atlanta, Ga.
Dr. Maurice C. Pincoffs, Baltimore, Md.
Dr. Anton J. Carlson, Chicago, Ill.
Dr. Henry A. Christian, Boston, Mass.

The report of the Committee on Public Relations was presented by Dr. Ernest E. Irons, Chairman. Among items under communications were the following:

A disciplinary recommendation from two Fellows concerning a member who had solicited x-ray contracts. The Committee considered this a matter which involves the question of ethics and recommended that it should be first dealt with by the local group and the county medical society; however, if College members in the district are not then satisfied, charges may be preferred against the member in accordance with Article XIV, Section 1 of the By-Laws of the College. (This recommendation was approved by the Regents.);

A proposal from the Hollywood Academy of Medicine that some sort of association of academies of medicine be formed for the distribution of speakers over the country. The Committee pointed out that the College already has committees to carry out its own program, and that its programs and ideals might considerably differ from those of other groups, and no action was recommended;

An inquiry from the Committee on Patents of the National Research Council, asking the attitude of the College in regard to the advisability of universities taking out patents. The Committee pointed out this question is distinctly a controversial one on which the College could make no pronouncement without extensive investigation, and that this question would seem to be without the province of the College;

Invitation from the Secretary of Labor, requesting the participation of the College on the President's Committee on "National Employ the Physically Handicapped Week." The Committee recommended that the College shall accept the invitation;

Letters and correspondence between Dr. Howard C. Naffziger, of the American College of Surgeons, and President Hugh J. Morgan, concerning means by which nursing education and increase in nursing services can be obtained. The Committee on Public Relations recognizes there is a shortage of nurses in all categories, and recommended that a Committee of three be appointed by the President of the American College of Physicians to consult with the Committee of the American Medical Association, of which Dr. Thomas Murdock, F.A.C.P., a Governor of our College, is the Chairman, and with similar committees of the American College of Surgeons and the Hospital Associations. (This was approved by the Regents by formal resolution, and President Morgan appointed Dr. Francis G. Blake, Chairman, Dr. Walter W. Palmer and Thomas Murdock.);

On the recommendation of the Committee, the dues of one Fellow were waived, due to physical disability; a former Surgeon General of the Navy, who became a Fellow of the College by reason of his position and as a service to the College, has now retired from said position and the Committee provided that his name may be automatically dropped from the Membership Roster; the resignations of Dr. William P. Chester (Associate), Detroit, Mich., and Dr. Charles A. Waters, F.A.C.P., Baltimore, Md., were accepted.

Report, Committee on Educational Policy, Dr. William S. Middleton, Chairman: The Committee on Educational Policy of necessity crosses many lines. I trust our

ruminations and recommendations may not be assumed to be presumptive in certain instances. In the first place, we were privileged to have a preview of the President's program for San Francisco. It is a very comprehensive one, and all of you will miss something if you are not in attendance. There was, furthermore, a very clear definition of the policies and program of the Committee on Postgraduate Courses. Dr. Edward L. Bortz, in attendance at that meeting, gave us an outline of the courses that had been given and of courses proposed for the spring and autumn of 1948. There is in his hands the necessity of judging of general trends; apparently, psychosomatic medicine and chemotherapy are falling somewhat in favor, and those courses have been undersubscribed in certain areas. There was, however, a suggestion that a new opportunity be offered in psychosomatic medicine under Dr. Harold G. Wolff, of New York, N. Y. This is supported by the Committee on Educational Policy. There was, furthermore, the protest of certain Fellows of the College that courses of two weeks' duration are rather extended, requiring their absence from duties, and an expression of preference in the main for courses of one week. Occasionally, by special request, for example by Dr. Robert A. Cooke, of New York, ten days will be given in Allergy for a very limited group of six to eight physicians. The policy of charging fees to foreign attendants at Postgraduate Courses was discussed, and it is the recommendation of Dr. Bortz that at the discretion of the Director of a given course, foreign guests may be free or exempt from the routine fees. This, however, would be a matter of policy that we feel the Regents should pass upon. The Committee, however, feels that it is a wise and a fair gesture to individuals coming from countries where there is a marked differential in the exchange and where it is not possible to withdraw adequate funds for participation in such programs.

In relation to the composite consideration of the program of postgraduate medical education, there was the suggestion arising out of correspondence with Dr. George R. Herrmann that a course in Cardiology be conducted by Dr. Ignacio Chavez at Mexico City during the summer of 1948, or some succeeding summer. This received the support of the Committee on Educational Policy.

The matter of fellowships under the American College of Physicians has been an expanding program, and it is the feeling of the Committee that there be given consideration to foreign fellowships, that there be no limitation to American centers or of American leaders, but that our candidates be considered for training in foreign areas. This should probably be considered by the Committee on Fellowships and Awards.

There was latterly the consideration of the correspondence of Dr. Noble Wiley Jones relative to exchange professorships with Australia, but the sense of our Committee was that we might properly enter upon this project conservatively through the recommendation to the Regents that there be invited from time to time from any foreign country distinguished guests who would address the American College of Physicians at its Annual Meeting. It was the further suggestion that such individuals, if known to the College at large, might become the guest or visiting professors to any one of our medical colleges. This would, of course, be the responsibility of the respective universities, and not of the American College of Physicians.

There was lastly the advice to the Regents that it is the sense of the Committee on Educational Policy that a gracious gesture would be made in inviting several English speaking colleagues to attend our Annual Meetings.

. . . On motion by Dr. William D. Stroud, regularly seconded and carried, the report and recommendations of the Committee on Educational Policy were approved.

. . .

Report, Editor, ANNALS OF INTERNAL MEDICINE, Dr. Maurice C. Pincoffs: The ANNALS, judging by its circulation, is meeting the approval of the profession, to the satisfaction of the Editor, and, I hope, to the members of the Board. Our chief

problem at the present time is the paper shortage, which we had hoped would be alleviated long ago, but which is about as serious as it ever was. Consequently, the numbers of the ANNALS are slimmer than we would like to have them, and slimmer than the material that comes in would warrant. The manuscripts now received show in general a much higher standard of quality, and there is a larger number than even before the War. On the average, we receive about thirty-five papers and fifteen case reports a month. We publish about eight general papers and from three to five case reports. We have made a special effort to raise the standard of our editorials. We have gone afield from the Editors, although Dr. Clough contributes very heavily, to men in special fields to write editorials, and I hope they are occasionally read and considered a valuable feature of the journal. Any question of expansion of the ANNALS itself, or any other publication that the College might wish to undertake, must be deferred until it would be feasible from the point of view of facilities. The Annals Committee has discussed those matters in a tentative way. One that occurred to us for the future is the possibility of publishing all the Morning Lectures. At present we are able to accept only a few Morning Lectures. These Lectures are generally too lengthy, and sometimes it is difficult to get all the manuscripts. However, there is a demand for them, and some of them are very valuable.

We encounter trouble in getting out the journal on time, and I think my office has to take part of the onus for that, but it also lies to some extent with the difficulties that our excellent printers, the Lancaster Press, have been having in War time and since. The speed with which they can convert a manuscript into a galley and turn the galley into page proof is distinctly less than formerly, and they are operating on a very tight schedule. They print a number of journals, and we, therefore, share the difficulty of getting our manuscripts through sufficiently far in advance. We now have in their hands, for example, all the accepted material for January and part of February, but even so we shall find that it is going to be difficult to get out these issues by the middle of the respective months. Progress is being made on getting back on schedule, and I hope that in 1948 we shall accomplish our aims in that direction.

Dr. Edward L. Bortz, Chairman, reported for the Advisory Committee on Postgraduate Courses, pointing out that during 1947 nineteen courses were given with an attendance of more than one thousand physicians. All courses had been substantially successful, and the Committee had noted a trend in interest, probably stimulated by the American Board of Internal Medicine, in returning to the refreshing experience in the basic studies. The most popular course the College had given was one on the Physiological Basis for Internal Medicine at Philadelphia, and the Committee was planning other similar courses in other parts of the country. Dr. Bortz then presented the schedule of Postgraduate Courses proposed for the spring of 1948 (this list already printed elsewhere in the ANNALS), and he proceeded to emphasize the importance of physicians acquainting themselves with the medical aspects of radioactivity. He said in part, "That field is of the greatest importance clinically, basically and from the standpoint of industrial hazards, because one of the most significant pronouncements that has been made since the end of the War was that of the distribution of Radioactive Isotopes at the Fourth International Cancer Congress in St. Louis during September. As these Radio Isotopes are being distributed, qualified personnel throughout the world for transit and handling at the site of origin where they are made and where they are being studied in industry is necessary; the field is expanding so rapidly, and the medical profession knows practically nothing about it. Doctors are not yet cognizant of the immediate importance of this field. When one considers the possibilities that may develop in our country in the future, one can appreciate the tremendous responsibility that might fall on the shoulders of the medical profession. We should awaken to the importance of having a sound understanding of the management of casualties due to radioactive substances. The course the College has

arranged through the courtesy and coöperation of the Navy will present an unusual opportunity for members to become better informed about radioactive substances and the biological effects of exposure to them."

Dr. Bortz further pointed out that his Committee and the Executive Secretary are studying the schedule of courses for the autumn of 1948, and even looking forward to two or three years ahead, noting courses that ought to be fitted into the College program at the appropriate time.

(The Board of Regents by resolution approved the report and the schedule of courses for the spring of 1948.)

Report, Conference Committee on Graduate Training in Medicine, Dr. Reginald Fitz, Chairman: Mr. President and members of the Board, the resolution introduced by Dr. Sloan and already passed epitomized the work of the Conference Committee. For the sake of the record, the Committee would like to report that it met both with the Council on Medical Education and Hospitals of the American Medical Association and with the American Board of Internal Medicine. The idea of having advice available from the College to these two bodies seemed to have been well received, though exactly how the College can contribute most appropriately is still undetermined. This report is submitted as one for progress and contains no recommendations.

. . . On motion by Dr. Reginald Fitz, regularly seconded and carried, the report was accepted. . . .

Report, Committee on Fellowships and Awards, Dr. Reginald Fitz, Chairman: Since the last meeting of the Board of Regents, the Committee on Fellowships and Awards has held several conferences by mail. It has selected Dr. Ernest W. Goodpasture, of Vanderbilt University, to receive the John Phillips Memorial Award for 1948. Not only has his work in virology been outstanding, but as a teacher, he has proved to be an inspiring leader to generations of medical students. The Committee believes his work has had a direct bearing upon the advancement of clinical science in this country, and that in every way he deserves the award.

A year ago the Board of Regents ruled that the Committee, after obtaining the advice of the President and others, should nominate to the Board at least four months before the next Annual Session a candidate to receive the James D. Bruce Memorial Award and to deliver the James D. Bruce Lecture. The candidate so nominated must be eminent in any of the many divisions of preventive medicine. The Committee, supported by the President, now nominates for this distinction in 1948, Dr. James S. Simmons, a Fellow of the College, formerly Chief of Preventive Medicine Service in the Surgeon General's Office, and the Army member of the President's Committee on Medical Research, O.S.R.D., and at present Dean of Harvard School of Public Health.

The Committee has made a study of the accomplishments of the College's Research Fellows. Of 16 Fellows appointed up to the beginning of the War, one has become a Professor of Medicine, one an Associate Professor, six Assistant Professors in medical faculties, and almost all the rest occupy positions weighted with research or teaching responsibilities. Such a record is impressive, yet the question arose as to whether candidates were being selected from a sufficiently wide field. With this thought in mind this year, the Committee has widely circulated announcements concerning the Fellowships. Thirty-seven applications from over the country were filed before the arbitrarily stipulated deadline of November 1, a far larger number than ever before. These applications have been sifted with all possible care, and from the list the Committee now recommends that seven Fellows be appointed to begin work on July 1, 1948, namely:

(1) James G. Campbell, a graduate of McGill University; $3,200.00.
(2) Frank H. Gardner, a graduate of Northwestern University; $2,200.00.

(3) Joseph E. Gianairacusa, a graduate of the University of California; $3,200.00.
(4) Samuel P. Martin, a graduate of Washington University; $3,200.00.
(5) Peritz Scheinberg, a graduate of Emory University; $3,000.00.
(6) Lutfu L. Uzman, a graduate of Harvard University; $2,200.00.
(7) John M. Weller, a graduate of Harvard University; $3,200.00.

On the first day of July, 1948, $10,266.67 will remain in the unexpended Research Fellowship Fund. The Committee asks for an additional appropriation of $10,200.00, making an entirely available fund of $20,466.67, to be available for Fellowships from July 1, 1948, to June 30, 1949.

The candidates nominated are young men, and several have had their normal careers interrupted by periods of military service. The Committee believes that they represent a group of unusual promise and seriousness of purpose. The differences in stipend take into consideration the financial needs of each candidate and the number of his dependents.

In accordance with the vote of the Board of Regents on April 29, 1947, the Committee has chosen Dr. John M. Weller to be known as the Alfred Stengel Research Fellow of the College for 1948. Of the Fellows nominated, he appears to offer promise of attaining great distinction in investigation and teaching, and as a clinician. I move the acceptance of this report and the adoption of the recommendations of the Committee.

. . . Motion was duly seconded and carried. . . .

Dr. Francis G. Blake, Chairman, reported for the Committee on the ANNALS OF INTERNAL MEDICINE, making the following points:

(1) The Committee, with the authorization of the Executive Committee, had approved the increase of approximately 8 per cent in the printing costs from August 1, 1947, amounting to approximately $2,500.00 per annum currently;
(2) The last two complete volumes, XXV and XXVI, for the year ending June 30, 1947, had produced a surplus of $32,328.49, and the average circulation had increased nearly 2,000 copies per month;
(3) The Committee felt the content of the ANNALS with respect to original articles, case reports and editorials had been highly satisfactory; the number of pages devoted to news notes and miscellaneous material had been reduced from 400 pages to 326 pages; the Editor had reported an adequate and satisfactory supply of material for publication; increase in the size of the journal has been restricted solely due to limitation of available paper, but as soon as additional supplies are available, the number of pages per issue shall be increased; the Committee recommends a better quality of paper as soon as it is available;
(4) A special effort should be made to restore the regular publication schedule, so that the ANNALS shall appear by the sixteenth of each month;
(5) The Committee had reviewed the Editor's budget, and had recommended its approval to the Finance Committee.

(The Regents, by resolution, accepted and approved the report.)

Report, House Committee, Dr. William D. Stroud, Chairman: Mr. President and members of the Board of Regents, it is recommended by the House Committee that the Board of Regents formally authorize the setting up of a Building Fund Reserve for the following, which has been tentatively authorized and approved by the Board at the meeting of April 27, 1947. This is not a budget appropriation per se and is not chargeable against 1948 income.

Contract with R. M. Shoemaker Company for construction of new addition to College Headquarters Building		$48,880.00
Less: Reduction for using Indiana limestone instead of architectural tile		900.00
		$47,980.00
Architect's Fee, 6% (Trumbauer Co.)		2,878.80
Extras (Estimated):		
Laying New Telephone Conduit	$ 125.00	
Lighting Fixtures	800.00	
Floor Covering, General Office (plastic tile or rubber)	1,000.00	
Miscellaneous (unforeseen emergencies)	2,216.20	4,141.20
		$55,000.00

. . . On motion by Dr. William D. Stroud, regularly seconded and carried, the above recommendation was unanimously approved. . . .

The House Committee was consulted about the possibility of providing at the College Headquarters temporary space for the American Academy of Allergy, on a donation basis of an appropriate fee, possibly from $70.00 to $80.00 per month. This would not be on a true rental basis. The Committee met with the Executive Secretary, who feels that after we occupy the new wing of the new Building, two rooms on the second floor might be made available to the Academy on a "cancellable basis," satisfactory to both organizations. The American Academy of Allergy is considering moving their headquarters from New York to Philadelphia, but have not actually come to a conclusion.

DR. PAULLIN: Should not any such arrangement for occupying space be subject to cancellation, possibly on sixty days' notice?

DR. FITZ: Is there any question of the legality of the procedure. I should like to make sure that any arrangement is above reproach.

DR. TENNEY: The New York Academy of Medicine houses several other societies in its Building, but that does not affect its income tax status.

PRESIDENT MORGAN: I would assume that any arrangement that is worked out to implement the motion we are considering will be done with the advice of the attorneys of the College.

. . . On motion by Dr. William D. Stroud, regularly seconded and carried, this second portion of the report of the House Committee was approved. . . .

Report of the Treasurer, Dr. William D. Stroud: On October 31, 1947, the Cash Balance of the College was as follows:

Endowment Fund	$ 3,013.27
General Fund	124,725.23
	$127,738.50

The Finance Committee will make recommendations concerning the investment of the balance in the Endowment Fund and of $10,000.00 additional from the General Fund.

The Finance Committee will report the record of security transactions since the last meeting of this Board.

Present security holdings of the College are as follows:

	Book Value	*Market Value*	*Appreciation*
Endowment Fund	$253,941.62	$266,397.75	$12,456.13
General Fund	146,441.18	163,211.25	16,770.07
	$400,382.80	$429,609.00	$29,226.20

The approximate annual cash income from these securities amounts to $16,000.00, an average yield of 3.84 per cent.

The services of our Investment Counselor, Drexel & Co., appear to your Treasurer to be entirely satisfactory. At the last meeting of the Board of Regents, the Treasurer was instructed to attempt to persuade the Investment Counselor to be more conservative in their proposed increased service charge, and I am glad to report that effective July 1, 1947, the charge was increased to $300.00 per year, rather than to $400.00, as they had proposed earlier. The arrangement is subject to termination by either party at any time, and in all other respects the agreement remains in effect as first made on December 30, 1940.

. . . On motion by Dr. William D. Stroud, regularly seconded and carried, the report was accepted. . . .

Report, Committee on Finance, Dr. Charles F. Tenney, Chairman: The Committee on Finance met with the Executive Secretary and Treasurer on November 22, 1947, and reports as follows:

(1) The following transactions have been executed since the last meeting of the Board of Regents:

Sold

Endowment Fund

		Cost	*Sold For*	*Gain*
7–10–47	5,000 Chicago & Western Indiana Railroad Co., Consolidated, 4s, due 1952	$5,225.25	$5,241.25	$16.00

Called

General Fund

		Cost	*Called For*	*Gain*
9–30–47	50 Shares, American Brake Shoe & Foundry Co., 5¼%, Cum.	$6,163.60	$6,250.00	$86.40

Purchases

Endowment Fund

7–10–47	50 Shares, Atlantic Refining Co., $3.75, Pfd., Cum., "B"	$5,080.00
7–10–47	20 Shares, Liggett & Myers Tobacco Co., Common "B"	1,830.00
7–11–47	6,000 United States of America Savings Bonds, 2½s, Series "G", due July 1, 1959	6,000.00
10– 6–47	20 Shares, Texas Company	900.00

General Fund

10–21–47	50 Shares, New York Power & Light, $3.90, Pfd.	5,067.50

(2) The Committee examined in detail the analysis of the College holdings by its Investment Counselor, Drexel & Co., and approves their recommendations for the following:

For the General Fund:

5,000 New York, New Haven and Hartford Railroad Co., Harlem River & Port Chester Division, 4s, 5–1–54, at par

20 Shares, E. I. du Pont de Nemours & Co., common, at 189

Also, the conversion of Phillips Petroleum Co. rights to appropriate stock purchases in the approximate amount of $1,300.00.

For the Endowment Fund:

80 Shares, General Electric Co., Capital Stock, at approximately 37

The Committee examined in detail the operating statements and budgets prepared by the Executive Secretary and herewith submitted to the Board. The first three pages of the operating statements represent experience through October 31, 1947, and pages four and five represent estimated income and expenditures to the end of the year. It is anticipated from these statements that there will be a surplus for 1947, exclusive of the building program, of approximately $48,000.00. It may be pointed out that the income for 1947 was materially greater than anticipated for the following reasons:

(1) The Board of Regents returned the rate of dues to the original level of several years ago, which resulted in an increase from that source of $13,000.00.
(2) There were more members inducted to Fellowship, with an increase in the Initiation Fee account.
(3) The income from investments, likewise, was greater than anticipated.
(4) Subscriptions to the journal increased more than $14,000.00 over anticipations.
(5) A phenomenal number of Fellows subscribed to Life Membership.

(Dr. Tenney reviewed in detail the various departmental budgets, and after certain adjustments were made by the Board of Regents, a budget providing an estimated income of $193,830.00 and an estimated expenditure of $152,644.10 was adopted. Entirely separate from that budget was the appropriation to the College Building Fund of $55,000.00 authorized during 1947, but payable during 1948. The entire report, the financial statements for 1947 and the budgets for 1948 were by resolution approved by the Regents.)

Report, Joint Committee for the Coördination of Medical Activities, Dr. Ernest E. Irons, Chairman: This Committee has continued its meetings. About a year ago we asked the members whether it would be wise to discontinue the activities of the Committee, but there was a general protest on the part of almost everyone, and the feeling was expressed there would be certain advantages in having the general problems affecting medicine receive discussion and comment by all the member organizations, including the hospital associations, one of the large funds, the Armed Services, the Public Health Service, the Federal Security Administration, and practically all large organizations that have an interest in medicine. The College is represented by Dr. Walter L. Palmer and myself. The Minutes of the meetings are printed in the Journal of the American Medical Association, although occasionally somewhat delayed, due to paper shortages and also by reason of the fact that all of these Minutes must go to each representative for comment and approval before publication. On the whole, I think there is a distinct value attached to this Committee. It is no expense to the College.

PRESIDENT MORGAN: The last Committee report is that of the Consulting Committee on the Annual Sessions. I am glad to report that the General Sessions and

Morning Lectures have been arranged, and there remains only one or two vacant assignments to be settled.

(Dr. Morgan passed out copies of his Program.)

Dr. Alan Gregg, Director of the Medical Science Division of the Rockefeller Foundation, will be the Convocational Lecturer. I will now ask Doctors Kerr and Falconer, joint General Chairmen, for their reports.

DR. WILLIAM J. KERR: Mr. President, Officers and Regents, Dr. Morgan's program, as he has announced it, appears to us to be quite outstanding. Dr. Falconer and I have been working on the Panels and on the Clinics. The Panels are going to be held each noon, as in recent years, and the Morning Lectures will be confined to two mornings, with a double series each morning, and the Clinics will be consolidated into two mornings, held in several of the hospitals in San Francisco. This year the Clinics will actually be clinics. We are not planning to give any other demonstrations, or to carry on further series of lectures, etc., but everyone participating in the Clinic Sessions will be expected to discuss the problems of patients, and that will be the keynote. The Panels have been well worked up, although I cannot give you all the details at the moment. They will cover the main problems of medicine.

We are emphasizing, as we should in our part of the country, two features—one on infectious diseases, in which we have some preëminence in that part of the country, and the other on radioactive elements of the isotopes. This is one of the great important areas of knowledge in medical practice at the present time, and unless we are abreast of what is going on in that field, we shall be quite remiss in bringing things to the attention of the members of the College.

We hope we shall have a large attendance. In 1932, when the College last met in San Francisco, we were in the depths of the great depression, and there were only two hundred or so members who came to California from East of the Rocky Mountains. I am sure that will not be repeated this time. We are prepared to show all the members what is going on on the Pacific Coast.

Some of the details of entertainment have not yet been concluded. 1948 marks the centenary of the discovery of gold in California, and we think there is still gold "in them thar hills," and we are going to feature this celebration to some extent. Long years ago we had a visitor in California by the name of Robert Louis Stevenson, who was a great friend of the physician, and who had good reason to know physicians. It may be possible to do something in a small way to honor the name of that great man. At any rate, we hope to have some things in the way of entertainment which are unique. We may even be undignified at times, but your President has acquiesced and encouraged us to give you a good time. Dr. Falconer had to leave for a plane, and asked me to report for him as well.

Those of you who are coming by special train, or otherwise, may be able to visit some of the National Parks, or the redwood section of California, or the Yosemite; there are many things worth seeing if you have not seen them before.

PRESIDENT MORGAN: Some members have repeatedly asked that some method be worked out to record the Panel Discussions. The Panels are really one of the most interesting features of the Annual Session. They are informal, conducted by experts and are extremely informative. I would like to suggest that they may be reported in the ANNALS. That raises a question that has come up many times in our meetings, which, up to the present time, has not been solved. Everyone knows it is a fine idea, but it has produced problems that have been very difficult to meet. It is only a matter of recording what is said, and I suggest, Dr. Kerr, that you look into the possibility of using the soundscriber, or other recording device, if not for all the Panels, at least for certain Panels that you know are going to be of great interest. The record will have to be edited, and that might be an after meeting responsibility which you could pass on to some of the members of your department. It may cost us some money, but I

think we should attempt to determine if this can be successfully done. We will now hear the arrangements made by the Executive Secretary for the meeting.

Mr. Loveland reported that he had spent some days in San Francisco during June, making the necessary general arrangements. He reported on the matter of hotels, meeting rooms, the Technical Exhibit, meeting schedules of the Regents, Governors and Committees, the special trains to San Francisco, the post-convention trip to Hawaii, etc. There followed a discussion of the schedule of meetings of the Board of Governors and the Board of Regents, and it was finally agreed that the various Committees would meet on Saturday and Sunday morning, April 17–18, and the Board of Regents and Board of Governors would hold a joint executive session on Sunday afternoon, April 18, and that the schedule of other meetings of the two Boards be continued as heretofore. It was also suggested that the Chairman of the Committee on Credentials appear before a meeting of the Board of Governors to acquaint that Board with the problems and difficulties of handling candidates for membership.

By resolution, the meeting adjourned at 2:40 p. m.

Attest: E. R. LOVELAND,
Secretary

OBITUARIES

DR. MARION HERBERT BARKER

M. Herbert Barker, M.S., M.D., F.A.C.P., of Chicago, Ill., died suddenly on August 14, 1947, of a subarachnoid hemorrhage.

Dr. Barker was born in 1899 at Villisca, Iowa. He received a B.S. from the University of South Dakota in 1923, an M.D. from Rush Medical College in 1925, and an M.S. in Physiology from Northwestern University in 1930. His training included a two-year interneship at Wesley Memorial Hospital, Chicago, two years as assistant resident at the Peter Bent Brigham Hospital in Boston, and two years as resident at the Passavant Memorial Hospital in Chicago. He became an attending physician at the last institution in 1931 when he entered private practice.

Throughout his professional career Dr. Barker was active in teaching and research. At the time of his death he was Associate Professor of Medicine in the Northwestern University Medical School. His primary interest was in the field of cardiovascular-renal disease, although during the war he was responsible for much of the work done by the Army on infectious hepatitis. He published over 40 papers, many representing original contributions.

During World War I Dr. Barker served in the Marine Corps. In World War II he had nearly four years of active duty, two and one-half of which were in the Mediterranean Theater. As a Lieutenant Colonel and later as a Colonel he was Chief of Medicine in the 12th General Hospital. In 1944 he was appointed special consultant to the Theater Surgeon and received the Legion of Merit for his work on infectious hepatitis.

Dr. Barker was a member of many medical organizations including the Chicago Society of Internal Medicine, Chicago Institute of Medicine, Chicago Society of Medical History, Central Society for Clinical Research, Central Clinical Research Club, American Heart Association (Chairman of Peripheral Vascular Section in 1946), American Society for the Study of Arteriosclerosis (founding member), fellow of the American Medical Association, fellow of the American College of Physicians, and member of the Cardiac Society of Great Britain. In addition he was Chairman of the Committee for Nomenclature of Renal Vascular Disease, Regional Consultant in Internal Medicine to the Surgeon General of the United States Army and Chairman of the Board for the Study of Hepatitis, member of the Sub-committee on Diseases of the Liver of the National Research Council. He was a diplomate of the American Board of Internal Medicine, certified in internal medicine and cardiovascular disease.

Dr. Barker was endowed with tireless energy and vitality. He was not only an able physician and teacher but an astute investigator. In addition he was concerned with many organizational activities. His enthusiasm and vision made him a valued counselor. His loss will be keenly felt, not only in Chicago and among his friends, but among his many colleagues throughout the country.

RICHARD B. CAPPS, M.D., F.A.C.P.

DR. CHARLES J. BLOOM

Dr. Charles J. Bloom, a Fellow of the College since 1928, died at Touro Infirmary, New Orleans, on August 29, 1947, of heart disease.

Dr. Bloom, son of Albert and Rose (Dreyfous) Bloom, was born in New Orleans, October 23, 1886. He received his primary and secondary education in the public schools of New Orleans and attended Tulane University of Louisiana (B.S., 1908, and M.D., 1912). He served an externship at Charity Hospital of Louisiana, 1909–

1910, and an internship at Touro Infirmary, 1912–1914. He attended Harvard University for postgraduate courses 1914–1916.

His teaching, which covered a period of 35 years, began during his student days at Tulane as Instructor in Zoology, 1907, and Lecturer in Biology, 1908. He was Assistant in Hygiene in the Tulane School of Medicine, 1912–1914; Assistant in the laboratory of Hygiene and Clinical Assistant in Diseases of Children, 1914–1916; Instructor in Pediatrics, 1919–1920. In the Tulane Postgraduate School, where he became head of the Department of Pediatrics, he was Clinical Assistant in Diseases of Children, 1916–1918; Assistant Professor of Diseases of Children, 1918–1919; Professor of Diseases of Children, 1919–1925; Professor of Pediatrics, 1925 until his resignation, June 30, 1937. At Louisiana State University School of Medicine he was Professor of Pediatrics and head of the Postgraduate Department (1937–1939). He was also a member of the faculty of the Southern Pediatric Seminar, Saluda, N. C. (1924–1942).

He had served in attending or consultant capacity on the staff of practically every hospital in New Orleans, and at the time of his death was on the staffs of Charity Hospital of Louisiana (head of the Independent Pediatric Service), Touro Infirmary (former Secretary), Baptist Hospital, Lakeshore Hospital, French Hospital (Consultant), and Flint Goodridge Hospital of Dillard University (Consultant). Among his community interests he founded the Magnolia School for exceptional children in 1934 and served as its General Chairman. During the first World War he held the rank of First Lieutenant in the Medical Reserve Corps.

He was a member of the Orleans Parish and Louisiana State Medical Societies, the American Medical Association, Southern Medical Association, Louisiana State Pediatric Society; American Academy of Pediatrics, Pure Milk Society of New Orleans (board member), Society of Mental Hygiene, Beta Theta Pi, Nu Sigma Nu, Kappa Delta Phi, Alpha Omega Alpha, Stars and Bars, Tulane Alumni Association (one of representatives from the School of Medicine on the Executive Committee, 1942–1946).

Among his many contributions to medical literature, his book on "The Care and Feeding of Babies in Warm Climates" (1922, revised 1937) was widely used.

EDGAR HULL, M.D., F.A.C.P.,
Governor for Louisiana

DR. GEORGE CUMMINGS BOWER

George Cummings Bower, M.D., F.A.C.P., was born at Blasdell, N. Y., September 28, 1898. His medical degree was taken in the University of Buffalo in 1922, following which he interned in the Erie County and Deaconess Hospitals in Buffalo. He became Assistant Physician in the Willard State Hospital, Willard, N. Y., from 1924 to 1928, and subsequently served as Pathologist and Director of Clinical Laboratory in the Marcy State Hospital, Marcy, N. Y., from 1933 until his death. Dr. Bower was a Diplomate of the American Board of Pathology.

Dr. Bower was elected a Fellow of the American College of Physicians in 1934. He was also a member of the Geneva Academy of Medicine, the Seneca County and New York State Medical Societies, the New York State Society of Pathologists, and the American Medical Association.

Dr. Bower was highly respected for his scientific knowledge by his associates at the Marcy State Hospital. In his death the hospital has lost a very capable and efficient pathologist.

EDWARD C. REIFENSTEIN, SR., M.D., F.A.C.P.,
Governor for Western New York

DR. PERCY TILSON MAGAN

Percy Tilson Magan, M.D., F.A.C.P., was born on November 13, 1867, at Marlefield House in the County of Wexford, Ireland. He died on December 16, 1947, from a heart attack which was the terminal incident of a long illness.

At the age of seventeen years, Percy Magan, the eldest son and potential heir to an estate of considerable worth, left his home in Ireland, and came to America, landing on the day of Grant Ward Panic in May of 1884. Though times were hard and his economic status was not particularly good, he had previously decided to work out his own problems and to plan his own career. Traveling farther west to Nebraska, he worked as a farmhand for over a year.

While he had received a sound preliminary education at St. George's School in Huntingdon, England, he had become resentful of the strict discipline of the educational system and had no particular desire to receive further formal education. He became acquainted with many Seventh-day Adventists and eventually joined that church, in the interest of which he devoted all of his time and energy throughout the rest of his active life. His sincerity and devotion were exemplified by his adherence to his faith even though he was disinherited by his father. In 1888 he entered the Battle Creek College in Battle Creek, Mich., from which he graduated in 1893. Soon thereafter he accompanied S. N. Haskell, a leader in the Adventist Church, in a trip around the world to find suitable locations for the establishment of mission stations. He was Professor of History and the Bible in the Battle Creek College from 1891 to 1901, and established a reputation as a great teacher. Later, as its Dean, he entered the field of administration which he followed for the rest of his life. His reputation as a school administrator became widely recognized. In consideration of certain problems which were developing at the Battle Creek College, he and E. A. Sutherland were instrumental in moving the College to Berrien Springs, Mich.; it has since grown to be one of the strongest colleges in the Adventist educational system.

Dr. Magan and his close friend, E. A. Sutherland, developed a strong desire to establish self-supporting medical missionary work in the neglected South. In order to become better qualified to attain the objectives of such a project, both men decided upon a medical education. Dr. Magan received the M.D. degree cum laude in 1914 from the University of Tennessee College of Medicine. Doctors Magan and Sutherland then established a medical institution in connection with the Church's school at Madison, Tenn. This is still operating, and from this center there have developed some thirty smaller self-supporting rural schools and medical centers.

In the meantime, the College of Medical Evangelists had been started, and, on the recommendation of President Newton Evans, Dr. Magan was appointed Dean in 1915. He was made president in 1928 and president emeritus in 1942.

In less than two years, he succeeded in raising the rating of the school from class C to class B. The College continued to grow, its foundations have become more secure, and Dr. Magan is credited with bringing it to its present place among the medical schools of the land.

Dr. Magan was well known among American and British medical educators and leaders. Membership in many professional societies indicated his interest in the general field of medicine. These included the Chairmanship of the Anatomy Board, southern division, Department of Public Health, California; trustee, Medical Board of Los Angeles County General Hospital; member, Board of Trustees, Public Health League of California; Fellow, American Medical Association, Society of American Bacteriologists, American Hospital Association, League for Conservation of Public Health, National Tuberculosis Association, American Cancer Foundation, Southern California Medical Association, Clinical and Pathological Society of Los Angeles; ex-Vice President, California Medical Association; Trustee, Los Angeles County

Medical Association; Fellow, American College of Physicians, 1929. He was also editor of the Health Magazine.

Dr. Magan was an indefatigable worker, a man of strong convictions and of extraordinary ability. He devoted his life to the cause, and the things which he has said and the influence which he has had in the College of Medical Evangelists and in the lives of many who have been associated with him will long be remembered.

W. E. MacPherson, M.D., F.A.C.P.

DR. JOHN NATHAN SIMPSON

John Nathan Simpson, M.D., F.A.C.P., died on November 23, 1947, at the General Hospital, Morgantown, W. Va., following several years of illness. Dr. Simpson was 78 years old.

Born in Morrison, Ill., March 19, 1869, Dr. Simpson was a graduate of Peabody College for Teachers, Nashville, Tenn. (A.B., 1891) and of the Johns Hopkins University (M.D., 1902). In 1902 he founded the College of Medicine of West Virginia University as an organized two-year school. Prior to that time the University had offered courses in anatomy, physiology, and hygiene. Dr. Simpson served the College of Medicine as Professor of Anatomy and Physiology, as Professor of Medicine, and as Dean, until 1935 when he became Professor Emeritus and Dean Emeritus. In 1906 he studied in Paris and Vienna.

Dr. Simpson was Director of the Hygiene Laboratory of the State Department of Health from 1913 to 1917.

Dr. Simpson's society memberships included the American Academy of Medicine, American Medical Association, American Association for the Advancement of Science, Southern, Mongolia County and West Virginia State Medical Associations; he was president of the latter Society in 1923.

Dr. Simpson was one of the early members of the American College of Physicians, having been elected a Fellow in it and a member of the American Congress on Internal Medicine in 1921. In 1922 he became a member of the first Board of Governors of the College and served as Governor for West Virginia from that date to 1936.

DR. THOMAS E. WILLIAMS

Dr. Thomas E. Williams, of Shreveport, La., a Fellow of the American College of Physicians since 1926, died on October 4, 1947, of carcinoma of the prostate.

A native of Hillsboro, Ohio, and a graduate of the Jefferson Medical College of Philadelphia, Dr. Williams began practice in Marshall, Tex., but afterwards moved to Shreveport, where he was active in the medical and civic affairs of that city for many years. He enjoyed a large medical practice, but was also active as a member of the visiting staff of the Shreveport Charity Hospital. He was one of the founders of the Tri-State Hospital, and was chief of the medical staff of the Tri-State Clinic.

Dr. Williams was a member of the Shreveport, Louisiana State and Tri-State Medical Societies, the Southern Medical Association, and a Fellow of the American Medical Association. In 1926 he was elected a member of the American Congress on Internal Medicine.

Because of ill health Dr. Williams had been in semi-retirement for several years before his death.

Edgar Hull, M.D., F.A.C.P.,
Governor for Louisiana

PROGRAM

THE AMERICAN COLLEGE OF PHYSICIANS

Twenty-Ninth Annual Session

SAN FRANCISCO, CALIF.

April 19–23, 1948

GENERAL SESSIONS AND LECTURES

Hugh J. Morgan, President

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William J. Kerr and Ernest H. Falconer

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Anthony B. Diepenbrock, St. Mary's Hospital, San Francisco

Earl F. Evans, Captain, (MC), U.S.N., U. S. Naval Hospital, Oakland
Mack M. Green, Colonel, (MC), U.S.A., Letterman General Hospital, San Francisco
Gordon E. Hein, Veterans Administration, San Francisco
Stacy R. Mettier, University of California Hospital, San Francisco
John J. Sampson, Mount Zion Hospital, San Francisco
Edward B. Shaw, Children's Hospital, San Francisco
H. Clare Shepardson, Franklin Hospital, San Francisco
Michael B. Shimkin, Laguna Honda Hospital, San Francisco

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Theodore L. Althausen
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Harold G. Trimble

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INVITATION

Sixteen eventful years have elapsed since San Francisco was host to the American College of Physicians, in April, 1932. A very special and cordial welcome has accumulated during this period, and is extended to the members of the College for its Twenty-ninth Annual Session.

San Francisco as a civic institution, the San Francisco and Alameda County Medical Societies, the California Medical Society, the California Academy of Medicine, the medical schools and the hospitals of San Francisco and the Bay Region send greetings and are prepared to extend their facilities to the members and guests.

San Francisco has two Class A medical schools, Stanford University School of Medicine and the University of California Medical School. The former is the outgrowth of the old University of the Pacific founded by Elias S. Cooper in 1858. In 1882 Doctor Levi Cooper Lane built the first of the present medical school buildings on land donated by himself, and later constructed Lane Hospital. In 1908 this property was transferred to Leland Stanford Junior University and forms a nucleus of the present medical school. The University of California Medical School was founded by Doctor H. H. Toland in 1864. He transferred Toland Hall to the Regents of the University in 1873. It was not until 1902 that the Medical Department actually became part of the University. The campus of the Leland Stanford Junior University lies adjacent to the city of Palo Alto, 30 miles from San Francisco. The campus and buildings are readily accessible from the standpoint of transportation facilities and make a very interesting trip. The academic departments of the University of California are located in Berkeley. This campus is readily accessible and makes an interesting trip via the San Francisco-Oakland Bridge. In addition to the two medical schools with their hospitals, there are fourteen hospitals in San Francisco. These include the San Francisco Hospital, which is in reality a group of hospitals with its divisions: the Emergency Hospitals; the Psychiatric Department; the Tuberculosis Division; and the Laguna Honda Home, a hospital for elderly and chronically ill patients.

The famous cyclotron of the University of California is located in Berkeley and is operated in connection with the Physics Department located on that campus. A sizeable department of medical physics has developed in connection with the cyclotron and is located on the Berkeley campus. Also, a medical clinic has been developed in this connection, owing to the necessity of accommodating the patients who apply for various types of treatment with radioactive agents. These radioactive agents are also available and are utilized in the regular clinics at the Medical School in San Francisco. The Laboratory of Experimental Oncology was established at the Laguna Honda Home in January of 1947. It is a joint project of the National Cancer Institute, National Institute of Health, United States Public Health Service, Department of Public Health of the City and County of San Francisco and the University of California Medical School. This laboratory contains electrophysiologic equipment for the study of physiology in cancer patients, a biochemical-immunologic unit, and also a ward of 25 beds.

In addition to being the leading medical center on the Pacific Coast, San Francisco is famous for its beauty as a city and for its interesting environment. Situated by the Golden Gate and possessing two world-famous bridges, it has mountain scenery close at hand in Marin County across the Golden Gate Bridge. The redwoods of Muir Woods are near-by. The Valley of the Moon and the Spanish Missions are readily accessible by automobile. It is interesting to contemplate that, with improved air-travel facilities, it is possible to leave San Francisco in the morning and have dinner in the evening in the Hawaiian Islands. The Yosemite Valley is beautiful in the latter part of the month of April but is apt to be cool, particularly at night.

With the abundant opportunities for sight-seeing and entertainment and with the available facilities of our hospitals and medical schools, it is our hope and expectation that the 29th Annual Session of the College will prove of exceptional interest and satisfaction to the members and guests when they assemble here in San Francisco during the coming month of April.

GENERAL INFORMATION

GENERAL HEADQUARTERS

Civic Auditorium

Grove Street

Registration headquarters, information bureau, technical exhibits, general sessions, morning lectures, panel discussions, meetings of Board of Regents, Board of Governors and committees. Panel discussions will also be scheduled in the Third Floor Hall, Public Health Building, 101 Grove Street. The Annual Convocation and Banquet will take place in the Fairmont Hotel, 950 Mason Street.

HOTEL ACCOMMODATIONS

Ample accommodations have been allocated for the housing of members of the College and guests during the 1948 Annual Session. San Francisco, however, has no large hotels of the metropolitan type, but has many fine smaller hotels. Very few single rooms are available; members are urged to use double rooms. The hotels named below have officially promised accommodations, and will honor requests for reservations sent in directly by members and guests. The absence of quoted rates for single rooms indicates the hotel has guaranteed no single rooms. The various classes, A, B and C, in many instances indicate only comparison in size, for many Class B hotels are comparable with Class A hotels, although smaller. In requesting reservations, please state clearly date and time of anticipated arrival and departure; mention the fact that reservations are being made in connection with the Annual Session of The American College of Physicians; and enclose a check for $5.00 as deposit.

Officers, Regents, Governors, Speakers and Clinicians on the Program should address their requirements to Mr. E. R. Loveland, Executive Secretary, The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., who has reserved for this group adequate accommodations in the Mark Hopkins and Fairmont Hotels.

The Whitcomb Hotel, 1231 Market Street, will be the official headquarters of the technical exhibitors, who may make their reservations direct by communication with Mr. Charles Knapp, Manager.

OFFICIAL HOTELS

CLASS A RATING

CLIFT—Geary & Taylor Sts. †152
Double—$7.00, $8.00, $9.00
Twin—$8.00, $10.00, $12.00
Suites—$20.00, $25.00, $30.00

PALACE—Market & New Montgomery Sts. †330
Double—$8.00, $9.00, $11.00
Twin—$9.00, $10.00, $12.00
Suites—$18.00 to $35.00
Roll-away bed in any room, add $2.00

ST. FRANCIS—Union Square. †400
Double—$8.00, $9.50
Twin—$8.00, $9.50, $10.50, $12.00, $14.00
Two rooms, bath between—$18.00, $20.00
Each extra person, $2.50 a day

SIR FRANCIS DRAKE—450 Powell St. †375
Single—$6.00, $7.00, $8.00
Double—$8.00, $9.00, $10.00
Twin—$9.00, $10.00, $11.00
Each extra person, $2.00 a day

CLASS B RATING

BELLEVUE—Geary & Taylor Sts. †80
Double—$6.00
Twin—$6.50
Suites—$10.00

CALIFORNIAN—405 Taylor St. †118
Single—$3.00
Double—$5.25
Twin—$6.00
Suites—$12.00 (up to 4 persons)

CANTERBURY—750 Sutter St. †50
Double—$5.00, $6.00
Twin—$6.00, $6.50, $7.00
Each extra person, $1.00 a day

CHANCELLOR—433 Powell St. †80
Double—$5.00
Twin—$6.00
Each extra person, $1.00 a day

DRAKE-WILTSHIRE—340 Stockton St. †190
Single—$2.50, $3.00
Double—$4.00, $4.50, $5.00
Twin $6.00
Each extra person, $1.50

EMBASSY—610 Polk St. †24
Double—$4.00
Twin—$4.00
Each extra person, $1.50 a day

MANX—225 Powell St. †95
Single—$3.00, $3.50
Double—$4.00, $4.50
Twin—$5.00, $6.00

MAURICE—761 Post St. †22
Double—$5.00
Twin—$6.00
Suites—$10.00

PLAZA—Post at Stockton Sts. †40
Double—$5.00 to $6.00
Twin—$6.50 to $8.50

STEWART—351 Geary St. †100
Double—$4.00, $4.50
Twin—$4.50, $5.00
Suites—$8.00

CLASS C RATING

BALDWIN—321 Grant Ave. †22
Double—$4.00
Twin—$5.50

BARCLAY—235 O'Farrell St. †9
Single—$2.50
Double—$3.00
Twin—$3.50

BRAYTON—50 Turk St. †54
Double—$3.00*, $3.50, $4.00
Twin—$5.00
Two rooms, bath between—$6.50, $7.00, $8.00
Each extra person, $1.00 per day

CARLTON—1075 Sutter St. †20
Double—$3.50
Twin $4.00
Each extra person, $1.25 a day

† Gross number of accommodations (persons) guaranteed.

* Indicates without bath; otherwise, all rooms with private bath.

CARTWRIGHT—524 Sutter St. †50
Double—$4.00
Twin—$4.50
Each extra person, $1.00 a day

COLUMBIA—411 O'Farrell St. †30
Double or Twin—$3.50

COMMODORE—825 Sutter St. †50
Double—$6.00
Twin—$7.00

DEVONSHIRE—335 Stockton St. †25
Single—$2.50*
Double—$3.00*, $3.50, $4.50
Twin—$3.50*, $4.50, $5.00
Two rooms, bath between—$8.00
Suites—$12.00

EL CORTEZ—550 Geary St. †50
Single—$3.50, $4.00, $5.00
Double—$4.50, $5.00, $6.00
Twin—$6.00, $7.00
Each extra person, $1.00 a day

FEDERAL—1087 Market St. †57
Double—$2.50*, $3.50
Twin—$3.00*, $4.50
Two rooms, bath between—$6.50 to $7.00

FIELDING—Geary & Mason Sts. †40
Double—$5.00
Twin—$6.00

GOLDEN STATE—114 Powell St. †80
Double—$2.50*, $3.50
Twin—$5.00
Two rooms, bath between—$6.00
Each extra person, $1.50 a day

HERBERT—161 Powell St. †90
Double—$2.00 to $3.50*, $3.50 to $5.00
Roll-away bed in any room, add $1.50

KEYSTONE—54 Fourth St. †33
Single—$3.00
Double—$3.50
Twin—$5.00

LANKERSHIM—55 Fifth St. †100
Double—$2.50*, $3.50

† Gross number of accommodations (persons) guaranteed.
* Indicates without bath; otherwise, all rooms with private bath.

LOMBARD—1015 Geary St. †50
Double—$5.00
Twin—$6.50

NEW ALDEN—333 Fulton St. †15
Double—$2.50, $3.00, $3.50
Room with 1 double and 1 single bed—$4.00
Room with 2 double beds—$4.50

OLYMPIC—230 Eddy St. †60
Double—$4.00 to $5.00
Twin—$4.50 to $5.50

PICKWICK—5th & Mission Sts. †120
Double—$4.00, $4.50, $5.00
Twin—$4.50, $5.00, $5.50
Each extra person, $1.00 a day

POWELL—17 Powell St. †58
Double—$4.00
Each extra person, $1.00 a day

ROOSEVELT—240 Jones St. †45
Single—$3.00, $3.50
Double—$3.50, $4.00
Each extra person, $1.00 a day

SENATE—467 Turk St. †45
Double—$3.00
Each extra person, $1.00 a day

SENATOR—519 Ellis St. †24
Double—$3.00
Twin—$4.00

SHAW—Market & McAllister Sts. †65
Single—$3.50
Double—$5.00
Twin—$6.00
Each extra person, $1.50 a day

SUTTER—Sutter & Kearney Sts. †50
Double—$5.00
Twin—$6.00

WASHINGTON—Grant Ave. & Bush St. †40
Double—$4.00, $4.50, $5.00
Twin—$4.50, $5.00, $5.50

† Gross number of accommodations (persons) guaranteed.

Who **May Register—**

(*a*) All members of The American College of Physicians in good standing for 1948.

(*b*) All newly elected members.

(*c*) Senior and graduate medical students pursuing courses at the University of California and Leland Stanford Junior University, without registration fee, *upon presentation of matriculation cards or other evidence of registration at these institutions;* exhibits, general sessions and morning lectures.

(*d*) Members of the staff, including internes, of the hospitals participating in the program, without registration fee, *upon presentation of proper identification;* exhibits, general sessions and morning lectures.

(*e*) Members of the Medical Corps of the Army, Navy and Public Health Services of the United States and Canada, without registration fee, *upon presentation of proper credentials.*

(*f*) Qualified physicians who may wish to attend this Session as visitors; such physicians shall pay a registration fee of $12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published) included within such fee.

Registration Bureau—While official registration will start on Monday morning, April 19, advance registration of members and exhibitors will be provided for within the main entrance of the Civic Auditorium on Sunday, April 18, from 2:30 to 5:00 in the afternoon. The Registration Bureau will be open through the week from 8:30 A.M. to 5:45 P.M.

Registration Blanks for All Clinics and Panel Discussions will be sent with the final program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

Bulletin Boards for special announcements will be located near the Registration Bureau in the Civic Auditorium.

Transportation—Local transportation arrangements are in charge of the Committee on Transportation, which will issue full information at the Meeting.

The General Business Meeting of the College will be held at 2:00 P.M., Thursday, April 22, immediately preceding the afternoon scientific session. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors and the annual reports will be received from the Secretary-General, Executive Secretary and Treasurer. The President-Elect, Dr. Walter W. Palmer, New York, N. Y., will be inducted into office.

Board and Committee Meetings—The following meetings are scheduled as indicated. With the exception of the dinner meeting (following paragraph) all meetings will be held in the Civic Auditorium. Special meetings will be announced and posted.

A dinner meeting of the Board of Regents and of the Board of Governors will be held at the Mark Hopkins Hotel, Sunday, April 18, at 7:00 P.M.

COMMITTEE ON CREDENTIALS

Saturday, April 17, 2:00 P.M., Room 108, 1st Floor

ADVISORY COMMITTEE ON POSTGRADUATE COURSES

Sunday, April 18, 9:30 A.M., Room 203, 2nd Floor

COMMITTEE ON FINANCE

Monday, April 19, 10:30 A.M., Room 108, 1st Floor

COMMITTEE ON PUBLIC RELATIONS

Monday, April 19, 11:30 A.M., Room 108, 1st Floor

JOINT MEETING: BOARD OF REGENTS AND BOARD OF GOVERNORS

Sunday, April 18, 2:00 P.M., Room 203, 2nd Floor

BOARD OF REGENTS

Tuesday, April 20, 12:00 M., Room 203, 2nd Floor*
Friday, April 23, 12:00 M., Room 203, 2nd Floor*

BOARD OF GOVERNORS

Wednesday, April 21, 12:00 M., Room 203, 2nd Floor*

SPECIAL TRAINS AND POST-CONVENTION TOURS

For the convenience of members and guests of the College, arrangements have been made with the Baltimore and Ohio, Burlington Route, Denver Rio Grande, Missouri Pacific, Western Pacific and Santa Fe Railroads for three special trains to and from the San Francisco Annual Session. Train No. 1, departing from New York on Wednesday, April 14, will serve those in the New England, Middle Atlantic and South Atlantic States as well as Eastern Ohio. Train No. 2, operated for the convenience of members in Eastern and Central Canada, Western New York, Michigan, Northwestern Ohio and Indiana, Illinois, Wisconsin, Minnesota and Iowa, will depart from Chicago Thursday morning, April 15. Train No. 3, serving the South and Southwest as well as West Virginia, Ohio, Indiana, Missouri, Kansas and Oklahoma, will leave Cincinnati Thursday morning, April 15, and proceed via St. Louis to Colorado Springs, at which point the three special trains converge, on Friday, April 16. Stops for sightseeing will be made in that city and in Salt Lake City. The three special trains proceed from Colorado Springs to San Francisco on a common schedule, arriving Sunday evening, April 18.

Members not served directly by these schedules are urged, whenever possible, to arrange their itineraries so that they may join one of the special trains at the most convenient point.

The special trains will leave San Francisco on Friday evening, April 23. There will be sight-seeing stops at the Yosemite Valley and at Los Angeles (where local members will have a program of entertainment and inspection for the two and a half days available). Stops will also be made at the Grand Canyon in Arizona and the Carlsbad Caverns, New Mexico. The three special trains will operate on the same schedule to Kansas City, Mo., at which point they will separate. Train No. 1 will

* Buffet Luncheon served.

arrive in New York Sunday morning, May 2. Train No. 2 will arrive in Chicago Saturday morning, May 1. Train No. 3 will arrive in St. Louis the morning of Saturday, May 1, and Cincinnati the evening of that same day.

The coöperating railroads have published a special bulletin of the official itinerary, which includes information concerning schedules, rates, accommodations and special features. This bulletin will be mailed with the final program to all members of the College; others may obtain copies of the bulletin by addressing Mr. W. P. Cox, Baltimore & Ohio R. R., Broad and Walnut Sts., Philadelphia 9, Pa., through whom all accommodations on these special trains will be reserved.

POST-CONVENTION AIR CRUISE TO THE HAWAIIAN ISLANDS

For those who wish to visit Hawaii after the Annual Session, two all-expense air cruises from San Francisco have been planned. Both will leave by Pan American Clipper on Saturday morning, April 24. One cruise will occupy seven days, with return to San Francisco on Saturday, May 1; the other, ten days, returning to San Francisco on Tuesday, May 4.

Full information concerning these cruises is contained in the special trains bulletin referred to in the section above.

TO HAWAII BY SHIP

Many members of the College have indicated their interest in a cruise to Hawaii by water, either one or both ways. However, at the time of publication, no information had been received on the basis of which adequate steamship service could be predicted or guaranteed. It is possible that adequate ship accommodations may be established by the Matson Line by the time of the Annual Session. Information on this point may also be secured from Mr. Cox.

SPECIAL FEATURES

Monday, April 19, 1948

The Entertainment Committee has arranged for a **concert by the San Francisco Symphony Orchestra** under the direction of the celebrated conductor, Pierre Monteux, who has arranged a program which should have a wide appeal. The concert will begin at 8:15 P.M., in the auditorium of the Veterans' Memorial Building on Van Ness Avenue. Tickets may be obtained only at the Registration Bureau on Monday, April 19, and will be limited to Fellows and Associates of the College. No more than two tickets can be issued to a Fellow or Associate; two tickets may be issued to those accompanied by a member of the family. No reservations can be made in advance, and tickets will be available on the basis of first come, first served.

Wednesday, April 21, 1948

THE ANNUAL CONVOCATION OF THE COLLEGE—8:30 P.M., Ballroom, Fairmont Hotel. All members of the College and their families, and those of the public who are interested, are invited. All physicians elected Fellows of the College since the 1947 Convocation, and all previously elected Fellows who have not been formally inducted, should be present. Officers, Regents, Governors and new Fellows to be inducted, are requested to assemble in the Ballroom Annex, Fairmont Hotel, at 7:45 P.M., preparatory to the formation of the procession. They will be

conducted to their seats by the Marshal of the Convocation, Dr. T. Grier Miller, promptly at 8:30 P.M. It is suggested that all appear in evening clothes.

The Convocation ceremony will include the President's address and a Convocational Oration, "The Golden Gate of Medicine," by Dr. Alan Gregg, Director of the Medical Sciences of The Rockefeller Foundation, New York, N. Y. The John Phillips Memorial Medal for 1948, the James D. Bruce Memorial Medal for 1948, and the Alfred Stengel Diploma for 1948, will be awarded. The recipients of Research Fellowships of the College for 1948 will be announced. Also, Masterships will be conferred upon five outstanding Fellows of the College. The newly elected Fellows will be presented by the Secretary-General, Dr. George Morris Piersol, and, after subscribing to the Fellowship Pledge, will be inducted by the President. Following the Convocation, after a brief intermission during which guests will retire to the Lobby while the Ballroom is cleared, the President's Reception and Dance will take place in the Ballroom. All members and guests are requested to pass along the receiving line.

Thursday, April 22, 1948

A SPECIAL CEREMONY has been arranged **to honor the memory of Robert Louis Stevenson** whose residence in California had a beneficial influence on California Life. At 5:30 P.M., a brief ceremony will be held at the Stevenson Monument in Portsmouth Square. Mr. Joseph R. Knowland, Chairman of the State Park Commission, will make a few appropriate remarks. President Hugh J. Morgan will lay a wreath on the monument and speak briefly in tribute to the memory of one who, although he had occasion to encounter many physicians during his long period of disability, could still speak of the physician in the most commendatory manner.

THE ANNUAL BANQUET will be held in the Ballroom of the Fairmont Hotel at 8:00 P.M. Professor Frederick C. Woellner, Dean of the School of Education of the University of California at Los Angeles, will be the speaker of the evening on the subject, "A Philosophy of Trouble." Dr. William J. Kerr will be the Toastmaster.

All members of the College, physicians of San Francisco and surrounding area, visitors attending the Session, guests and friends, with their families, are cordially invited. Table reservations for groups may be arranged. Orchestral music will be furnished, and the evening has been planned as a most delightful occasion. Tickets should be purchased at the Registration Bureau by Wednesday afternoon, so that adequate preparations can be consummated.

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The Ladies' Entertainment Committee has prepared a program which, it hopes, will be interesting and enjoyable to all. The guests are requested to register at the Ladies' Headquarters in the Lobby of the Mark Hopkins Hotel on their arrival in San Francisco. Registration will start on Sunday afternoon, April 18, and continue each day thereafter through April 22.

Tickets for the various entertainment features will be procurable at the time of registration and, as accommodations at some of these are limited, early registration is advisable.

Programs will be available at the time of registration and the Committee will be prepared to offer maps and lists of theaters, shops, restaurants and places of interest in and about San Francisco.

Monday, April 19, 1948

9:00 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Afternoon: 3:00 to 5:00. Welcoming Tea, Fairmont Hotel.

Evening: 8:15. San Francisco Symphony Orchestra. (See under Special Features for Monday.)

Tuesday, April 20, 1948

9:00 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Morning: 9:30 to 1:30 P.M. San Francisco Bay Cruise. Buses to leave the Mark Hopkins Hotel at 9:30 and to return to the hotel at 1:30 P.M. Price of cruise, including bus fare from and to the hotel, $2.60. Light luncheon may be had on board at extra cost, if desired.

Wednesday, April 21, 1948

9:30 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Afternoon: 12:00 to 2:00. Luncheon and Fashion Show at the Palace Hotel. Price, $3.00.

Evening: 8:30. Convocation and President's Reception and Dance, Ballroom, Fairmont Hotel.

Thursday, April 22, 1948

9:30 A.M. to 4:00 P.M.: Registration, Lobby, Mark Hopkins Hotel.

Afternoon: Bus tour of San Francisco and Tea at the St. Francis Yacht Club. Buses to leave the Mark Hopkins Hotel at 1:00, arriving at the St. Francis Yacht Club for tea at 4:00, and returning to the hotel at 5:00. Those desiring to attend the Stevenson Ceremony in Portsmouth Square at 5:30 P.M., before returning to the hotel, should sign up with Mrs. LeRoy H. Briggs at the Registration Desk. Price of Tour, including Tea, $3.75.

Evening: 8:00. Annual Banquet of The College, Ballroom, Fairmont Hotel.

On Tuesday and Wednesday afternoons, conducted tours of Gump's and Chinatown will be arranged, if desired. Register with Mrs. LeRoy H. Briggs at Registration Desk.

Arrangements have been made for any members so desiring to play golf at the San Francisco Golf Club on Tuesday, April 20. Green fees, $2.00 a person. Transportation will be furnished. To make arrangements, call Mrs. George S. Johnson, Fillmore 6–6700, or apply at Registration Desk.

THE TECHNICAL EXHIBIT

The Technical Exhibit will be located in the Arena, ground floor of the Civic Auditorium.

The Committee on Exhibits of the College maintains highest possible standards in the conduct of this Exhibit. Exhibitors are admitted only by invitation; irrelevant

products are eliminated, and only firms which present a group of approved products of scientific interest to the internist and allied specialists may exhibit. Questionable methods of selling are prohibited.

The exhibitor's aim is to announce new products and to present new and interesting information to members and guests of the College. Likewise, many exhibitors take advantage of this opportunity to give aid and service directions to members who have previously adopted their products. Furthermore, this Exhibit provides the only convenient and direct method of contacting, personally, members of the College.

Members and guests of the College are encouraged to accord the exhibitors courteous and interested attention, thus recognizing their contributions to the Meeting and the effort that they make and the expense to which they go in building superior displays and furnishing, freely, valuable information.

The Technical Exhibit will be open during the following hours:

Monday, April 19..... 8:30 A.M. to 5:45 P.M.
Tuesday, April 20.....10:30 A.M. to 5:45 P.M.
Wednesday, April 21..... 8:30 A.M. to 5:45 P.M.
Thursday, April 22.....10:30 A.M. to 5:45 P.M.
Friday, April 23..... 8:30 A.M. to 2:45 P.M.

Special intermissions have been arranged, providing additional time for the inspection of the exhibits.

1948 EXHIBITORS

Abbott Laboratories, North Chicago, Ill.
American Association of University Presses
Ames Company, Inc., Elkhart, Ind.
Armour Laboratories, The, Chicago, Ill.
Ayerst, McKenna & Harrison, Limited, New York, N. Y.
Becton, Dickinson & Co., Rutherford, N. J.
Bilhuber-Knoll Corp., Orange, N. J.
Blakiston Company, The, Philadelphia, Pa.
Bristol Laboratories, Inc., New York, N. Y.
Burdick Corporation, The, Milton, Wis.
Burroughs Wellcome & Co. (U.S.A.), Inc., Tuckahoe, N. Y.
Cambridge Instrument Co., Inc., New York, N. Y.
Cameron Surgical Specialty Company, Chicago and New York
Camp & Company, S. H., Jackson, Mich.
Carnation Company, Oconomowoc, Wis.
Ciba Pharmaceutical Products, Inc., Summit, N. J.
Collins, Inc., Warren E., Boston, Mass.
Commercial Solvents Corp., New York, N. Y.
Cutter Laboratories, Berkeley, Calif.
Davies, Rose & Company, Limited, Boston, Mass.
Davis Company, F. A., Philadelphia, Pa.
Devereux Schools, Devon, Pa., and Santa Barbara, Calif.
Doak Company, Inc., Cleveland, Ohio
Doho Chemical Corporation, The, New York, N. Y.
Electro-Physical Laboratories, Inc., New York, N. Y.
Fleet Company, Inc., C. B., Lynchburg, Va.
General Electric X-Ray Corporation, Milwaukee, Wis.

Gerber Products Company, Fremont, Mich.
Grune & Stratton, Inc., New York, N. Y.
Harrower Laboratories, Inc., The, Glendale, Calif.
Heinz Co., H. J., Pittsburgh, Pa.
Hoeber, Inc., Paul B., New York, N. Y.
Hoffmann-LaRoche, Inc., Nutley, N. J.
Hollister-Stier Laboratories, Spokane, Wash.
Hygeia Nursing Bottle Co., Inc., The, Buffalo, N. Y.
Jones Metabolism Equipment Co., Chicago, Ill.
Kalak Water Co. of New York, Inc., New York, N. Y.
Lea & Febiger, Philadelphia, Pa.
Lederle Laboratories, Inc., Pearl River, N. Y.
Lilly and Company, Eli, Indianapolis, Ind.
Lippincott Company, J. B., Philadelphia, Pa.
Macmillan Company, The, New York, N. Y.
Maltine Company, The, New York, N. Y.
Mead Johnson & Company, Evansville, Ind.
Medical Bureau, The, Chicago, Ill.
Medical Film Guild, New York, N. Y.
Medical Protective Company, The, Fort Wayne, Ind.
Merck & Co., Inc., Rahway, N. J.
Merrell Company, The Wm. S., Cincinnati, Ohio
Mosby Company, The C. V., St. Louis, Mo.
Parke, Davis & Company, Detroit, Mich.
Picker X-Ray Corporation, New York, N. Y.
Pitman-Moore Company, Indianapolis, Ind.
Procter & Gamble Company, The, Cincinnati, Ohio
Reed & Carnrick, Jersey City, N. J.
Sanborn Company, Cambridge, Mass.
Sandoz Chemical Works, Inc., New York, N. Y.
Saunders Company, W. B., Philadelphia, Pa.
Schenley Laboratories, Inc., New York, N. Y.
Schering Corporation, Bloomfield, N. J.
Searle & Co., G. D., Chicago, Ill.
Sharp & Dohme, Incorporated, Philadelphia, Pa.
Smith-Dorsey Company, The, Lincoln, Nebr.
Smith, Kline & French Laboratories, Philadelphia, Pa.
Squibb & Sons, E. R., New York, N. Y.
Stacey, Inc., J. W., San Francisco, Calif.
Technicon Company, The, New York, N. Y.
Upjohn Company, The, Kalamazoo, Mich.
U. S. Vitamin Corporation, New York, N. Y.
Varick Pharmacal Company, Inc., New York, N. Y.
Warner & Co., Inc., William R., New York, N. Y.
Westwood Pharmacal Corp., Buffalo, N. Y.
Whirlpool Carriage, Inc., Westport, Conn.
White Laboratories, Inc., Newark, N. J.
Winthrop-Stearns Inc., New York, N. Y.
Wyeth Incorporated, Philadelphia, Pa.
Year Book Publishers, Inc., The, Chicago, Ill.

OUTLINE OF THE SAN FRANCISCO SESSION

Civic Auditorium events and rooms are indicated in bold type

TIME	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY
	April 19	**April 20**	**April 21**	**April 22**	**April 23**
9:00 A.M. to 11:30 A.M.	Morning free. **Registration, Exhibits, etc. (Arena)**	Hospital Clinics	**Morning Lectures* (Polk & Larkin Halls) 9:30–11:30**	Hospital Clinics	**Morning Lectures* (Polk & Larkin Halls) 9:30–11:30**
12:00 M. to 1:15 P.M.		**Panel Discussions (Polk, Larkin, Rm. 403)** (also Health Bldg.)	**Panel Discussions (Polk, Larkin, Rm. 403)** (also Health Bldg.)	**Panel Discussions (Polk, Larkin, Rm. 403)** (also Health Bldg.)	**Panel Discussions (Polk, Larkin, Rm. 403)** (also Health Bldg.)
2:00 P.M. to 5:25 P.M.	**1st General Session (Polk Hall)**	**2nd General Session (Polk Hall)**	**3rd General Session (Polk Hall)**	**Annual Business Meeting 4th General Session (Polk Hall)**	**5th General Session (Polk Hall)**
8:00 P.M. to 11:00 P.M.	San Francisco Symphony Concert		Convocation, followed by President's Reception (Ballroom, Fairmont Hotel)	Annual Banquet (Ballroom, Fairmont Hotel)	

* Two simultaneous series.

Note: Exhibits will be open on Monday and Wednesday from 8:30 A.M. to 5:45 P.M.; on Tuesday and Thursday, from 10:30 A.M. to 5:45 P.M.; on Friday, from 8:30 A.M. to 2:45 P.M.

GENERAL SESSIONS PROGRAM

Polk Hall, Civic Auditorium

FIRST GENERAL SESSION

Monday Afternoon, April 19, 1948

General Chairmen, William J. Kerr, F.A.C.P., and Ernest H. Falconer, F.A.C.P.
Dr. Kerr presiding

P.M.

2:00 **Invocation:**

Reverend HARLEY H. GILL, D.D., Superintendent of Northern California Congregational Conference.

Addresses of Welcome:

The Honorable ELMER E. ROBINSON, Mayor of San Francisco.
J. C. GEIGER, F.A.C.P., Director of Public Health.
ROBERTSON WARD, F.A.C.S., President of the San Francisco County Medical Society.
WILLIAM G. DONALD, President of the Alameda County Medical Society.
JOHN W. CLINE, F.A.C.S., President of the California Medical Association.
LOREN R. CHANDLER, F.A.C.S., Dean, Stanford University School of Medicine.
F. SCOTT SMYTH, F.A.A.P., Dean, University of California Medical School.

Response to Addresses of Welcome:

HUGH J. MORGAN, F.A.C.P., President of The American College of Physicians.

President Hugh J. Morgan, F.A.C.P., presiding

2:30 **The James D. Bruce Lecture on Preventive Medicine: The Challenge of Preventive Medicine.**

JAMES STEVENS SIMMONS, F.A.C.P., Brigadier General, (MC), U.S.A., Ret., Dean and Professor of Public Health, The Harvard School of Public Health, Boston, Mass.

3:15 INTERMISSION.

3:35 **Revisions in the Concept of Disease.**

KARL A. MENNINGER (by invitation), Manager, Winter Veterans Administration Hospital; General Director, Department of Education, The Menninger Foundation; Topeka, Kans.

3:55 **The Alarm Reaction and the Diseases of Adaptation.**

HANS SELYE (by invitation), Professor and Director of the Institut de Médecine et de Chirurgie Expérimentales, Université de Montréal, Montreal, P.Q., Can.

4:15 **Hypertension as a Reaction to Situational Threats: Experimental Study of Variations in Blood Pressure and Renal Blood Flow.**

STEWART G. WOLF, JR. (by invitation), Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, The New York Hospital; New York, N. Y.

4:35 Psychotherapeutic Blunders.

HENRY M. THOMAS, JR., F.A.C.P., Associate Professor of Medicine, Johns Hopkins University School of Medicine; Visiting Physician, Johns Hopkins Hospital; Baltimore, Md.

4:55 The Newer Analgesic Drugs: Their Use and Abuse.

HARRIS ISBELL (Associate), Director of Research, U. S. Public Health Service Hospital, Lexington, Ky.

5:15 ADJOURNMENT.

Monday Evening

PROGRAM OF ENTERTAINMENT

Arranged by the San Francisco Committee

Consult announcement concerning Special Features, page 503

SECOND GENERAL SESSION

Tuesday Afternoon, April 20, 1948

Polk Hall, Civic Auditorium

Presiding Officer
Walter W. Palmer, F.A.C.P., New York, N. Y.

P.M.

2:00 Skeletal Lesions in Hodgkin's Disease.

ERNEST H. FALCONER, F.A.C.P., Clinical Professor of Medicine, Chief of Hematologic Clinic, University of California Medical School, San Francisco, Calif.

2:20 Observations on Relapses in Pernicious Anemia.

EDGAR JONES, F.A.C.P., Associate Professor of Clinical Medicine, Vanderbilt University School of Medicine; Associate Visiting Physician, Vanderbilt University Hospital; Nashville, Tenn.

2:40 Radioactive Isotopes in Medicine.

JOHN H. LAWRENCE (by invitation), Chairman, Division of Medical Physics, University of California, Berkeley, Calif.

3:00 The Medical Aspects of Radiation Sickness.

STAFFORD L. WARREN (by invitation), Dean and Professor of Biophysics, University of California at Los Angeles School of Medicine, Los Angeles, Calif.

3:20 INTERMISSION.

3:40 Water Balance in Heart and Kidney Disease.

F. R. SCHEMM, F.A.C.P., Head of the Department of Internal Medicine, Great Falls Clinic, Great Falls, Mont.

4:00 **Therapeutic Use of Sodium, Potassium, and Phosphorus Solutions in Medical Emergencies.**

GEORGE W. THORN, F.A.C.P., Hersey Professor of the Theory and Practice of Physic, Harvard Medical School; Physician-in-Chief, Peter Bent Brigham Hospital; Boston, Mass.

4:20 **Fat Absorption in the Digestive Tract and the Use of Surface Acting Agents.**

CHESTER M. JONES, F.A.C.P., Clinical Professor of Medicine, Harvard Medical School; Physician, Massachusetts General Hospital; Boston, Mass.

4:40 **Prevention of Recurrences in Peptic Ulcer.**

THEODOR L. ALTHAUSEN, F.A.C.P., Professor of Medicine and Chief of Gastrointestinal Clinic, University of California Medical School, San Francisco, Calif.

5:00 ADJOURNMENT.

THIRD GENERAL SESSION

Wednesday Afternoon, April 21, 1948

Polk Hall, Civic Auditorium

Presiding Officer
Reginald Fitz, F.A.C.P., Boston, Mass.

P.M.

2:00 **The John Phillips Memorial Lecture: The Intracellular Environment for Infectious Agents.**

ERNEST W. GOODPASTURE (by invitation), Professor of Pathology and Dean, Vanderbilt University School of Medicine, Nashville, Tenn.

2:45 **Bacterial Resistance to Antibiotics.**

C. PHILLIP MILLER, F.A.C.P., Professor of Medicine, University of Chicago, Chicago, Ill.

3:05 INTERMISSION.

3:25 **Present Position of Our Knowledge of Anterior Pituitary Hormones.**

HERBERT M. EVANS (by invitation), Director, Institute of Experimental Biology, University of California, Berkeley, Calif.

3:45 **Diagnostic Significance of Hormones Excreted in the Urine.**

ROBERTO F. ESCAMILLA, F.A.C.P., Associate Clinical Professor of Medicine, University of California Medical School, San Francisco, Calif.

4:05 **The Differential Diagnosis of the Symptom Amenorrhea.**

HANS LISSER, F.A.C.P., Clinical Professor of Medicine, University of California Medical School; Chief of D-Unit, University of California Hospital Outpatient Department; Chief of Service, Endocrinology and Diabetes, Franklin Hospital; San Francisco, Calif.

4:25 Radioiodine and Graves' Disease.

MAYO H. SOLEY (by invitation), Professor of Medicine, University of California Medical School; Associate Visiting Physician, University of California Hospital; San Francisco, Calif.

4:45 Use of Estrogens in Medicine.

ELMER L. SEVRINGHAUS, F.A.C.P., Consultant in Endocrinology, Gouverneur Hospital, New York, N. Y., and Hospital of St. Barnabas and for Women and Children, Newark, N. J. (Montclair, N. J.).

5:05 Androgen Therapy.

WILLARD O. THOMPSON, F.A.C.P., Clinical Professor of Medicine, University of Illinois College of Medicine; Attending Physician, Grant and Henrotin Hospitals; Chicago, Ill.

5:25 ADJOURNMENT.

ANNUAL CONVOCATION

Wednesday Evening, April 21, 1948

8:30 o'Clock

Ballroom, Fairmont Hotel

T. GRIER MILLER, Marshal

All members of the profession and the general public are cordially invited. No admission tickets required.

1. Invocation.
   The Right Reverend KARL MORGAN BLOCK, D. D., Bishop of California Protestant Episcopal Church.
2. The President's Address: "Professio."
   HUGH J. MORGAN.
3. Presentation of Newly Elected Fellows and Recital of the Pledge.
   GEORGE MORRIS PIERSOL, Secretary-General.
4. Presentation of Newly Elected Masters.
5. Presentation of the John Phillips Memorial Medal for 1948.
6. Presentation of the James D. Bruce Memorial Medal for 1948.
7. Presentation of the Alfred Stengel Memorial Award for 1948.
8. Announcement of Research Fellows for 1948–49.
9. Convocational Oration: "The Golden Gate of Medicine."
   ALAN GREGG, Director of the Medical Sciences of The Rockefeller Foundation, New York, N. Y.

PRESIDENT'S RECEPTION

The President's Reception and Dance will follow one-half hour after this program, time being required to re-set the ballroom. A cordial invitation is extended to all members and guests, with their families.

FOURTH GENERAL SESSION

Thursday Afternoon, April 22, 1948

Polk Hall, Civic Auditorium

P.M.

2:00 THE ANNUAL BUSINESS MEETING.

All Fellows and Masters are urged to be present and to participate more actively in the administrative problems of the College. Reports will be received from the Secretary-General, Executive Secretary and the Treasurer; elections of new Officers, Regents and Governors will take place; President-Elect Walter W. Palmer, of New York, N. Y., will be inducted as President and will make a brief inaugural address.

Presiding Officer

Francis G. Blake, F.A.C.P., New Haven, Conn.

2:40 The Physiologic Effects of Physical Therapy.

George Morris Piersol, M.A.C.P., Vice Dean for Medicine and Professor of Medicine, Graduate School of Medicine, and Professor of Clinical Medicine, School of Medicine; Director, Center for Research and Instruction in Physical Medicine; University of Pennsylvania, Philadelphia, Pa.

3:00. INTERMISSION.

3:20 Infectious Arteritis.

William S. Middleton, F.A.C.P., Professor of Medicine and Dean of the Medical School, University of Wisconsin; Physician, State of Wisconsin General Hospital; Madison, Wis.

3:40 Streptomycin in the Treatment of Tuberculosis.

J. Burns Amberson, F.A.C.P., Professor of Medicine, College of Physicians and Surgeons, Columbia University; Visiting Physician-in-Charge, Chest Service, Bellevue Hospital; New York, N. Y.

4:00 The Pathogenesis of Rheumatic Fever.

William J. Kerr, F.A.C.P., Professor of Medicine and Chairman of the Division of Medicine, University of California Medical School, San Francisco, Calif.

4:20 Pathogenesis of Coccidioidomycosis.

Charles E. Smith (by invitation), Professor of Public Health and Preventive Medicine, Stanford University School of Medicine; Expert Consultant to The Surgeon General; San Francisco, Calif.

4:40 Empyema: Factors Involved in Recovery Following Local Penicillin Therapy.

WILLIAM S. TILLETT (by invitation), Professor of Medicine and Chairman of Department, New York University College of Medicine; Director, Third Medical Division, Bellevue Hospital; New York, N. Y.

5:00 The Pathogenesis of Human Brucellosis with Respect to Prevention and Treatment.

WESLEY W. SPINK, F.A.C.P., Professor of Medicine, University of Minnesota Medical School, Minneapolis, Minn.

5:20 ADJOURNMENT.

FIFTH GENERAL SESSION

Friday Afternoon, April 23, 1948

Polk Hall, Civic Auditorium

Presiding Officer
Walter L. Palmer, F.A.C.P., Chicago, Ill.

P.M.

2:00 Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions.

NORMAN E. FREEMAN, F.A.C.S. (by invitation), Associate Clinical Professor of Surgery, University of California Medical School, San Francisco, Calif.

2:20 Results of Extensive Thoraco-lumbar Sympathectomy for Hypertension.

JAMES A. EVANS, F.A.C.P., Physician, Department of Medicine, Lahey Clinic, Boston, Mass.

2:40 The Hemodynamic Effects of Sympathectomy.

ROBERT W. WILKINS (by invitation), Associate Professor of Medicine, Boston University School of Medicine; Assistant Director, Evans Memorial and Massachusetts Memorial Hospitals; Boston, Mass.

3:00 Essential Familial Hypercholesterolemia.

CHARLES F. WILKINSON, JR. (by invitation), Assistant Professor of Internal Medicine, University of Michigan Medical School, Ann Arbor, Mich.

3:20 INTERMISSION.

3:40 Clinical Aspects of the Acute Episode in Coronary Disease.

HERMANN L. BLUMGART (by invitation), Professor of Medicine, Harvard Medical School; Physician-in-Chief, Beth Israel Hospital; Boston, Mass.

4:00 The Capillary Factor in Ischemic, Asphyxic and Anoxic Myocardial Injury.

GEORGE R. MENEELY, F.A.C.P., Assistant Professor of Medicine, Vanderbilt University School of Medicine; Director of the Heart Station, Vanderbilt University Hospital; Nashville, Tenn.

4:20 Coronary Artery Occlusion in Man and Animals Studied by Radioactive Isotopes.

MYRON PRINZMETAL (by invitation), Senior Attending Physician and Director of Beaumont Laboratory for Cardiovascular Disease, Cedars of Lebanon Hospital, Los Angeles, Calif.

4:40 The Use of the Anticoagulants in the Treatment of Diseases of the Heart and Blood Vessels.

IRVING S. WRIGHT, F..A.C.P., Associate Professor of Clinical Medicine, Cornell University Medical College; Associate Attending Physician, The New York Hospital; New York, N. Y.

5:00 ADJOURNMENT.

MORNING LECTURES

The Morning Lectures recognize the increasing interest in fundamental problems and are planned to supplement the subject matter of the General Sessions. The Lectures enable the speaker to cover his presentation fully and to utilize charts, slides, motion pictures and other media to amplify his presentation.

Morning Lectures will be offered on Wednesday and Friday mornings only; Hospital Clinics on Tuesday and Thursday mornings only. Two series of Morning Lectures will be presented concurrently in Polk and Larkin Halls, Civic Auditorium. The scheduling of the Lectures and the proximity of the two halls make it possible for an auditor to attend a part of each program if he so elects.

The Lectures will be open to all members and guests of the College.

Admission by regular registration badge; no special tickets.

Wednesday, April 21, 1948

Polk Hall, Civic Auditorium

Presiding Officer
Charles T. Stone, F.A.C.P., Galveston, Tex.

A.M.

9:30–10:20 The Animal Kingdom, a Reservoir of Disease.

KARL F. MEYER (by invitation), Director of the George Williams Hooper Foundation for Medical Research and Professor of Bacteriology, University of California, San Francisco, Calif.

10:20–10:40 INTERMISSION.

10:40–11:30 Problems in the Natural History of Poliomyelitis.

ALBERT B. SABIN (by invitation), Professor of Research Pediatrics, University of Cincinnati College of Medicine and The Children's Hospital Research Foundation, Cincinnati, Ohio

Larkin Hall, Civic Auditorium

Presiding Officer
William S. McCann, F.A.C.P., Rochester, N. Y.

9:30–10:20 **Experimental and Clinical Therapeutic Studies on Lymphosarcoma.**
C. P. RHOADS, F.A.C.P., Director, Memorial Hospital and the Sloan-Kettering Institute for Cancer Research, New York, N. Y.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Etiology and Management of the Hemorrhagic Diatheses.**
CHARLES A. DOAN, F.A.C.P., Professor of Medicine and Dean, College of Medicine; Director of Starling-Loving University Hospital; Director of Medical Research; The Ohio State University, Columbus, Ohio.

Friday, April 23, 1948

Polk Hall, Civic Auditorium

Presiding Officer
William D. Stroud, F.A.C.P., Philadelphia, Pa.

A.M.

9:30–10:20 **Our Changing Viewpoint on Congestive Failure.**
ISAAC STARR (by invitation), Professor of Therapeutic Research and Dean, University of Pennsylvania School of Medicine, Philadelphia, Pa.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Management of the Failing Heart.**
HARRY GOLD (by invitation), Professor of Clinical Pharmacology, Cornell University Medical College; Attending Physician-in-Charge of the Cardiovascular Research Unit, Beth Israel Hospital; Attending Cardiologist to Hospital for Joint Diseases; New York, N. Y.

Larkin Hall, Civic Auditorium

Presiding Officer
Maurice C. Pincoffs, M.A.C.P., Baltimore, Md.

9:30–10:20 **Syndromes of Abdominal Pain of Medical Origin Simulating Acute Surgical Conditions.**
ARTHUR L. BLOOMFIELD, F.A.C.P., Professor of Medicine, Stanford University School of Medicine, San Francisco, Calif.

10:20–10:40 INTERMISSION.

10:40–11:30 **The Prognosis and Treatment of Hepatic Insufficiency.**
CECIL JAMES WATSON, F.A.C.P., Professor of Medicine, University of Minnesota Medical School; Physician-in-Chief, University Hospitals; Minneapolis, Minn.

DEMONSTRATION TOURS

Wednesday, April 21, 1948

9:00 to 11:00 A.M.

Buses with maximum capacity of 40 will leave Post Street entrance of St. Francis Hotel at 8:00 A.M. Buses are scheduled to return to the Auditorium by 12:00 noon. Cost of each tour, $1.00. Reservations cannot be made in advance by mail, but tickets will be on sale (first come, first served) at the Clinic Ticket Desk at the Registration Headquarters at the Civic Auditorium.

Tour 1. (Capacity, 40) **Demonstration at the Institute of Experimental Biology Laboratory,** Dr. Herbert M. Evans, Director, Room 4579, Life Sciences Bldg., University of California, Berkeley.

Tour 2. (Capacity, 40) **Visit to Radiation Laboratories, University of California, Berkeley,** under the direction of Dr. John H. Lawrence. This tour consists of seeing research in progress in the Crocker Laboratory, and viewing the sixty-inch cyclotron; also visiting the Donner Laboratory, there to be shown various phases of research. If circumstances permit, the 184-inch cyclotron will be seen in operation.

Tour 3. (Capacity, 40) **Demonstration at The Western Regional Laboratory, Department of Agriculture, Albany,** under the direction of Dr. Floyd DeEds. Research is being conducted on new uses for food products.

Tour 4. (Capacity, 40) **Visit to Stanford University. Hoover Library for War, Revolution and Peace, Exhibit on Russian Medicine,** under the direction of Dr. George H. Houck, F.A.C.P.

PANEL DISCUSSIONS

The Panel Discussions for the 29th Annual Session are concerned with topics of intimate interest and practical value to all members of the profession. Especially qualified men have been chosen as leaders and members of the panel personnel. These discussions will be held in the Civic Auditorium and in the third floor hall of the Public Health Building from 12:00 M. to 1:15 P.M., Tuesday, Wednesday, Thursday and Friday.

Applications for tickets to Panel Discussions are to be made by members on the regular application forms accompanying the formal program. Tickets will also be available at the Registration Bureau, Main Entrance, Civic Auditorium. Tickets will not be required for admission to Panel Discussions in Polk and Larkin Halls in view of the ample seating capacities of these rooms.

Applicants may submit in writing through the Executive Secretary of the College any questions concerning any phase of the subjects in which they are especially interested. Moderators and panel personnel will answer those questions which they feel are applicable to the subject under discussion, and will answer as many questions as time permits.

PANEL DISCUSSIONS

	Polk Hall Civic Auditorium (Admission by badge; no tickets.)	Larkin Hall Civic Auditorium (Admission by badge; no tickets.)	Room 403 Fourth Floor Civic Auditorium (Admission by ticket only.)	Third Floor Hall §Public Health Bldg. (Admission by ticket only.)
Capacity	1,200	800	200	240
Tuesday April 20 12:00 M. to 1:15 P.M.	**I** **Electrocardiography** Moderator *George C. Griffith Pasadena *George E. Burch New Orleans *Robert L. King Seattle Maurice Sokolow San Francisco *William D. Stroud Philadelphia William Paul Thompson Los Angeles	**II** **Gastrointestinal Disease** Moderator *Philip W. Brown Rochester, Minn. *John H. Fitzgibbon Portland, Ore. Leon Goldman San Francisco *Chester M. Jones Boston *Walter L. Palmer Chicago	**III** **Pulmonary Malignancy** Moderator *Sidney J. Shipman San Francisco *J. Burns Amberson New York *H. Corwin Hinshaw Rochester, Minn. *H. McLeod Riggins New York *John H. Skavlem Cincinnati *Julius L. Wilson New Orleans	**IV** **Virus Diseases** Moderator Karl F. Meyer San Francisco William McD. Hammon San Francisco W. Paul Havens, Jr. Philadelphia Albert B. Sabin Cincinnati
Wednesday April 21 12:00 M. to 1:15 P.M.	**V** **Anticoagulant Therapy in Coronary Disease** Moderator *Irving S. Wright New York *Nelson W. Barker Rochester, Minn. Herrman L. Blumgart Boston *George R. Meneely Nashville *E. Sterling Nichol Miami John J. Sampson San Francisco	**VI** **Hematology** Moderator *Charles A. Doan Columbus, Ohio *Edgar Jones Nashville *Stacy R. Mettier San Francisco *Edwin E. Osgood Portland, Ore. *Cyrus C. Sturgis Ann Arbor *Maxwell M. Wintrobe Salt Lake City	**VII** **Allergy** Moderator *Francis M. Rackemann Boston *J. Harvey Black Dallas *Ernest L. MacQuiddy Omaha *Albert H. Rowe San Francisco *John M. Sheldon Ann Arbor *Frank A. Simon Louisville, Ky.	**VIII** **Chemotherapy** Moderator *Chester S. Keefer Boston *H. Corwin Hinshaw Rochester, Minn. John Scott Hunt Lexington, Ky. Lowell A. Rantz San Francisco *Wesley W. Spink Minneapolis

§ 101 Grove St., across the street from the Civic Auditorium. * F.A.C.P.

PANEL DISCUSSIONS—*Continued*

	Polk Hall Civic Auditorium (Admission by badge; no tickets.)	Larkin Hall Civic Auditorium (Admission by badge; no tickets.)	Room 403 Fourth Floor Civic Auditorium (Admission by ticket only.)	Third Floor Hall §Public Health Bldg. (Admission by ticket only.)
Capacity	1,200	800	200	240
Thursday April 22 12:00 M. to 1:15 P.M.	**IX** **Hypertension, Medical and Surgical Aspects** Moderator *Edgar V. Allen Rochester, Minn. Winchell McK. Craig Rochester, Minn. Kenneth G. Kohlstaedt Indianapolis Howard C. Naffziger San Francisco Myron Prinzmetal Beverly Hills Robert W. Wilkins Boston	**X** **Endocrine Disease** Moderator *Hans Lisser San Francisco *Charles W. Dunn Philadelphia *Thomas H. McGavack New York *E. Kost Shelton Los Angeles *Willard O. Thompson Chicago *George W. Thorn Boston *Henry H. Turner Oklahoma City	**XI** **Liver Disease** Moderator *Cecil J. Watson Minneapolis *T. L. Althausen San Francisco Gerson R. Biskind San Francisco Roy H. Turner New Orleans	**XII** **Communicable Diseases** Moderator Edward B. Shaw San Francisco Henry Brainerd San Francisco Paul M. Hamilton San Marino, Calif. *Conrad Wesselhoeft Boston
Friday April 23 12:00 M. to 1:15 P.M.	**XIII** **Recent Advances in Chest Diseases** Moderator *James J. Waring Denver *J. Burns Amberson New York *Arthur L. Bloomfield San Francisco Fred R. Harper Denver Hugh W. Mahon M.C., U.S.A., Denver	**XIV** **Kidney Disease** Moderator *Laurence E. Hines Chicago Frank Hinman San Francisco *Robert K. Maddock San Francisco *Ferdinand R. Schemm Great Falls	**XV** **Psychosomatic Medicine** Moderator *Franklin G. Ebaugh Denver *Ward Darley Denver *Edward D. Hoedemaker Seattle *Frederick Lemere Seattle Karl A. Menninger Topeka *Norman Reider San Francisco	**XVI** **Radioactive Isotopes in Medicine** Moderator John H. Lawrence Berkeley John W. Gofman Berkeley Charles Heidelberger Berkeley Hardin B. Jones Berkeley Joseph F. Ross Boston Robert S. Stone San Francisco

§ 101 Grove St., across the street from the Civic Auditorium. * F.A.C.P.

THE CLINIC SESSIONS

Clinics and demonstrations will be conducted on **Tuesday** and **Thursday only** from 9:00 A.M. to 11:30 A.M., and Morning Lectures, as previously stated, will be conducted on Wednesday and Friday mornings, thus eliminating competition between these two features of the program. Participating hospitals include:

A. University of California Hospital
B. Stanford University Hospitals
C. Children's Hospital
D. Franklin Hospital
E. Laguna Honda Home
F. Mount Zion Hospital
G. St. Luke's Hospital
H. St. Mary's Hospital
J. San Francisco Hospital
K. Letterman General Hospital
L. U. S. Naval Hospital
M. Veterans Administration Hospital

At several of these hospitals two or more clinics will be running concurrently. Adequate accommodations will be provided for all, but admission will require special tickets which will be issued to members in advance of the Session and to non-members directly at the Registration Bureau in the Civic Auditorium. Application forms for tickets for the clinics will accompany the formal program to all members.

Emphasis will be placed on clinics in the true sense of that word—that is, patients will be shown and discussed rather than having presentations of formal short papers. Scarcely any field of medicine of importance to the clinician has been omitted. In addition to the various aspects of internal medicine, there will be numerous offerings in the allied fields. Opportunities will be afforded for visitors to see patients at close range and observe hospital methods in San Francisco.

The detailed program of clinics is not published in the ANNALS OF INTERNAL MEDICINE due to its considerable length, but every detail will be published in the formal program and distributed to all members and to non-members on the official mailing list at the Executive Offices of the College approximately seven weeks in advance of the Session.